CARBAMIC ACID COMPOUNDS COMPRISING A PIPERAZINE LINKAGE AS HDAC INHIBITORS

RELATED APPLICATIONS

This application is related to (and where permitted by law, claims priority to) U.S. Provisional Application number 60/369,337 filed 03 April 2002, the contents of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

This invention pertains generally to the field of biologically active compounds, and more specifically to certain carbamic acid compounds which inhibit HDAC (histone deacetylase) activity. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit HDAC, and in the treatment of conditions mediated by HDAC, cancer, proliferative conditions, psoriasis, etc.

BACKGROUND

Throughout this specification, including any claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps, but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and any appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

Ranges are often expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

DNA in eukaryotic cells is tightly complexed with proteins (histones) to form chromatin. Histones are small, positively charged proteins which are rich in basic amino acids (positively charged at physiological pH), which contact the phosphate groups (negatively charged at physiological pH) of DNA. There are five main classes of histones, H1, H2A, H2B, H3, and H4. The amino acid sequences of histones H2A, H2B, H3, and H4 show remarkable conservation between species, whereas H1 varies somewhat, and in some cases is replaced by another histone, e.g., H5. Four pairs of each of H2A, H2B, H3, and H4 together form a disk-shaped octomeric protein core, around which DNA (about 140 base pairs) is wound to form a nucleosome. Individual nucleosomes are connected by short stretches of linker DNA associated with another histone molecule (e.g., H1, or in certain cases, H5) to form a structure resembling a beaded string, which is itself arranged in a helical stack, known as a solenoid.

The majority of histones are synthesised during the S phase of the cell cycle, and newly synthesised histones quickly enter the nucleus to become associated with DNA. Within minutes of its synthesis, new DNA becomes associated with histones in nucleosomal structures.

A small fraction of histones, more specifically, the amino side chains thereof, are enzymatically modified by post-translational addition of methyl, acetyl, or phosphate groups, neutralising the positive charge of the side chain, or converting it to a negative charge. For example, lysine and arginine groups may be methylated, lysine groups may be acetylated, and serine groups may be phosphorylated. For lysine, the $-(CH_2)_4-NH_2$ sidechain may be acetylated, for example by an acetyltransferase enzyme, to give the amide $-(CH_2)_4-NHC(=O)CH_3$. Methylation, acetylation, and phosphorylation of amino termini of histones which extend from the nucleosomal core affects chromatin structure and gene expression. (See, for example, Spencer and Davie, 1999).

Acetylation and deacetylation of histones is associated with transcriptional events leading to cell proliferation and/or differentiation. Regulation of the function of transcription factors is also mediated through acetylation. Recent reviews of histone deacetylation include Kouzarides, 1999 and Pazin et al., 1997.

The correlation between the acetylation status of histones and the transcription of genes has been known for over 30 years (see, for example, Howe et al., 1999). Certain

enzymes, specifically acetylases (e.g., histone acetyltransferase, HAT) and deacetylases (e.g., histone deacetylase, HDAC), which regulate the acetylation state of histones have been identified in many organisms and have been implicated in the regulation of numerous genes, confirming the link between acetylation and transcription. See, for example, Davie, 1998. In general, histone acetylation correlates with transcriptional activation, whereas histone deacetylation is associated with gene repression.

A growing number of histone deacetylases (HDACs) have been identified (see, for example, Ng and Bird, 2000). The first deacetylase, HDAC1, was identified in 1996 (see, for example, Tauton et al., 1996). Subsequently, two other nuclear mammalian deacetylases were found, HDAC2 and HDAC3 (see, for example, Yang et al., 1996, 1997, and Emiliani et al., 1998). See also, Grozinger et al., 1999; Kao et al., 2000; and Van den Wyngaert et al., 2000.

Eleven (11) human HDACs have been cloned so far:

HDAC1 (Genbank Accession No. NP_004955)
HDAC2 (Genbank Accession No. NP_001518)
HDAC3 (Genbank Accession No. O15379)
HDAC4 (Genbank Accession No. AAD29046)
HDAC5 (Genbank Accession No. NP_005465)
HDAC6 (Genbank Accession No. NP_006035)
HDAC7 (Genbank Accession No. AAF63491)
HDAC8 (Genbank Accession No. AAF73428)
HDAC9 (Genbank Accession No. AAK66821)
HDAC10 (Genbank Accession No. AAK84023)
HDAC11 (Genbank Accession No. NM_024827

These eleven human HDACs fall in two distinct classes: HDACs 1, 2, 3 and 8 are in class I, and HDACs 4, 5, 6, 7, 9, 10 and 11 are in class II.

There are a number of histone deacetylases in yeast, including the following:

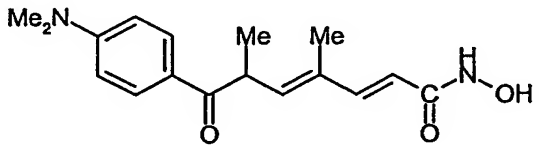
RPD3 (Genbank Accession No. NP_014069)
HDA1 (Genbank Accession No. P53973)
HOS1 (Genbank Accession No. Q12214)
HOS2 (Genbank Accession No. P53096)
HOS3 (Genbank Accession No. Q02959)

There are also numerous plant deacetylases, for example, HD2, in Zea mays (Genbank Accession No. AF254073_1).

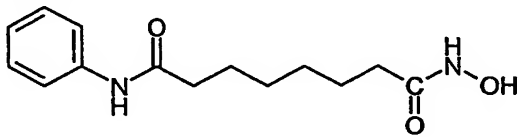
HDACs function as part of large multiprotein complexes, which are tethered to the promoter and repress transcription. Well characterised transcriptional repressors such as Mad (Laherty et al., 1997), pRb (Brehm et al., 1998), nuclear receptors (Wong et al., 1998) and YY1 (Yang et al., 1997) associate with HDAC complexes to exert their repressor function.

The study of inhibitors of histone deacetylases indicates that these enzymes play an important role in cell proliferation and differentiation. The inhibitor Trichostatin A (TSA) (Yoshida et al., 1990a) causes cell cycle arrest at both G1 and G2 phases (Yoshida and Beppu, 1988), reverts the transformed phenotype of different cell lines, and induces differentiation of Friend leukaemia cells and others (Yoshida et al., 1990b). TSA (and SAHA) have been reported to inhibit cell growth, induce terminal differentiation, and prevent the formation of tumours in mice (Finnin et al., 1999).

Trichostatin A (TSA)



Suberoylanilide Hydroxamic Acid (SAHA)



Cell cycle arrest by TSA correlates with an increased expression of gelsolin (Hoshikawa et al., 1994), an actin regulatory protein that is down regulated in malignant breast cancer (Mielnicki et al., 1999). Similar effects on cell cycle and differentiation have been observed with a number of deacetylase inhibitors (Kim et al., 1999).

Trichostatin A has also been reported to be useful in the treatment of fibrosis, e.g., liver fibrosis and liver cirrhosis. See, e.g., Geerts et al., 1998.

Recently, certain compounds that induce differentiation have been reported to inhibit histone deacetylases. Several experimental antitumour compounds, such as trichostatin A (TSA), trapoxin, suberoylanilide hydroxamic acid (SAHA), and phenylbutyrate have been reported to act, at least in part, by inhibiting histone deacetylase (see, e.g., Yoshida et al., 1990; Richon et al., 1998; Kijima et al., 1993). Additionally, diallyl sulfide and related molecules (see, e.g., Lea et al., 1999), oxamflatin (see, e.g., Kim et al., 1999; Sonoda et al., 1996), MS-27-275, a synthetic benzamide derivative (see, e.g., Saito et al., 1999; Suzuki et al., 1999; note that MS-27-275 was later re-named as MS-275), butyrate derivatives (see, e.g., Lea and Tulsyan, 1995), FR901228 (see, e.g., Nokajima et al., 1998), depudecin (see, e.g., Kwon et al., 1998), and m-carboxycinnamic acid bishydroxamide (see, e.g., Richon et al., 1998) have been reported to inhibit histone deacetylases. *In vitro*, some of these compounds are reported to inhibit the growth of fibroblast cells by causing cell cycle arrest in the G1 and G2 phases, and can lead to the terminal differentiation and loss of transforming potential of a variety of transformed cell lines (see, e.g., Richon et al., 1996; Kim et al., 1999; Yoshida et al., 1995; Yoshida & Beppu, 1988). *In vivo*, phenybutyrate is reported to be effective in the treatment of acute promyelocytic leukemia in conjunction with retinoic acid (see, e.g., Warrell et al., 1998). SAHA is reported to be effective in preventing the formation of mammary tumours in rats, and lung tumours in mice (see, e.g., Desai et al., 1999).

The clear involvement of HDACs in the control of cell proliferation and differentiation suggests that aberrant HDAC activity may play a role in cancer. The most direct demonstration that deacetylases contribute to cancer development comes from the analysis of different acute promyelocytic leukemias (APL). In most APL patients, a translocation of chromosomes 15 and 17 (t(15;17)) results in the expression of a fusion protein containing the N-terminal portion of PML gene product linked to most of RARα (retinoic acid receptor). In some cases, a different translocation (t(11;17)) causes the fusion between the zinc finger protein PLZF and RARα. In the absence of ligand, the wild type RARα represses target genes by tethering HDAC repressor complexes to the promoter DNA. During normal hematopoiesis, retinoic acid (RA) binds RARα and displaces the repressor complex, allowing expression of genes implicated in myeloid differentiation. The RARα fusion proteins occurring in APL patients are no longer responsive to physiological levels of RA and they interfere with the expression of the RA-inducible genes that promote myeloid differentiation. This results in a clonal expansion of promyelocytic cells and development of leukaemia. *In vitro* experiments have shown that

TSA is capable of restoring RA-responsiveness to the fusion RARα proteins and of allowing myeloid differentiation. These results establish a link between HDACs and oncogenesis and suggest that HDACs are potential targets for pharmaceutical intervention in APL patients. (See, for example, Kitamura et al., 2000; David et al., 1998; Lin et al., 1998).

Furthermore, different lines of evidence suggest that HDACs may be important therapeutic targets in other types of cancer. Cell lines derived from many different cancers (prostate, colorectal, breast, neuronal, hepatic) are induced to differentiate by HDAC inhibitors (Yoshida and Horinouchi, 1999). A number of HDAC inhibitors have been studied in animal models of cancer. They reduce tumour growth and prolong the lifespan of mice bearing different types of transplanted tumours, including melanoma, leukaemia, colon, lung and gastric carcinomas, etc. (Ueda et al., 1994; Kim et al., 1999).

Psoriasis is a common chronic disfiguring skin disease which is characterised by well-demarcated, red, hardened scaly plaques: these may be limited or widespread. The prevalence rate of psoriasis is approximately 2%, i.e., 12.5 million sufferers in the triad countries (US/Europe/Japan). While the disease is rarely fatal, it clearly has serious detrimental effects upon the quality of life of the patient: this is further compounded by the lack of effective therapies. Present treatments are either ineffective, cosmetically unacceptable, or possess undesired side effects. There is therefore a large unmet clinical need for effective and safe drugs for this condition.

Psoriasis is a disease of complex etiology. Whilst there is clearly a genetic component, with a number of gene loci being involved, there are also undefined environmental triggers. Whatever the ultimate cause of psoriasis, at the cellular level, it is characterised by local T-cell mediated inflammation, by keratinocyte hyperproliferation, and by localised angiogenesis. These are all processes in which histone deacetylases have been implicated (see, e.g., Saunders et al., 1999; Bernhard et al., 1999; Takahashi et al., 1996; Kim et al , 2001). Therefore HDAC inhibitors may be of use in therapy for psoriasis. Candidate drugs may be screened, for example, using proliferation assays with T-cells and/or keratinocytes.

Thus, one aim of the present invention is the provision of compounds which are potent inhibitors of histone deacetylases (HDACs). There is a pressing need for such

compounds, particularly for use as antiproliferatives, for example, anti-cancer agents, agents for the treatment of psoriasis, etc.

Such molecules desirably have one or more of the following properties and/or effects:

(a) easily gain access to and act upon tumour cells;

(b) down-regulate HDAC activity;

(c) inhibit the formation of HDAC complexes;

(d) inhibit the interactions of HDAC complexes;

(e) inhibit tumour cell proliferation;

(e) promote tumour cell apoptosis;

(f) inhibit tumour growth; and,

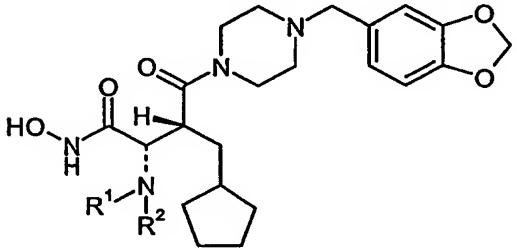
(g) complement the activity of traditional chemotherapeutic agents.

A number of carbamic acid compounds have been described.

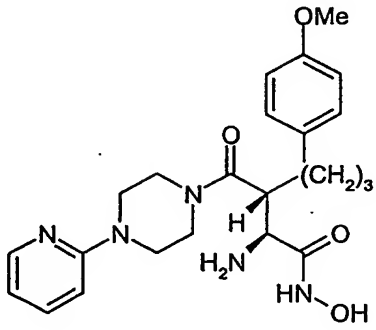
Certain classes of carbamic acid compounds which inhibit HDAC are described in Watkins et al., 2002a, 2002b, and 2002c.

Piperazino Amides

Alpegiani et al., 1999, describe compounds of the following type (Q^2 has backbone=2; is alkylene; is α-substituted) which are proposed to be useful in the treatment of diseases involving matrix metalloproteases (MMPs) and/or tumor necrosis factor α (TNF-α).

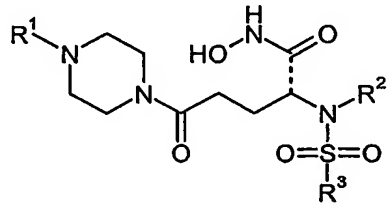


Alpegiani et al., 1999, also describes the following compound (Q^2 has backbone=2; is alkylene; is α-substituted):

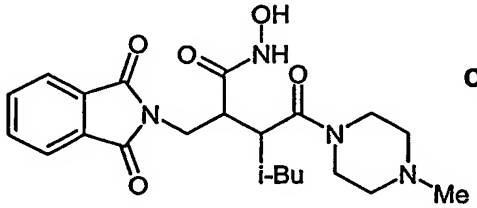


Example 42 (page 15)

Billedeau et al., 2000, describe compounds of the following type (wherein R^1 is, e.g., phenyl) (Q^2 has backbone=3; is alkylene; is α-substituted), which apparently inhibit procollagen C-proteinase, and are proposed for use in the treatment of fibrotic diseases.

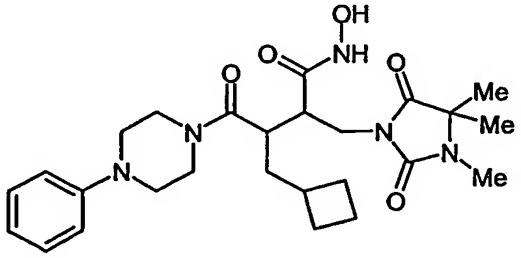


Broadhurst et al., 1993, describe the following compound (Q^2 has backbone=2; is alkylene; is α-substituted), which apparently inhibits collagenase.



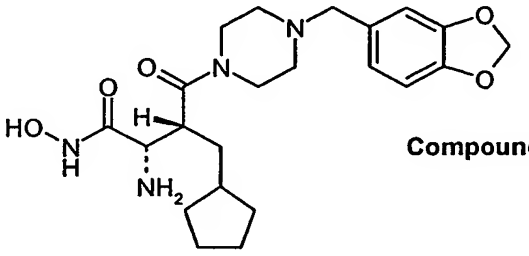
Compound F (page 9)

Broadhurst et al., 1995, describe the following compound (Q^2 has backbone=2; is alkylene; is α-substituted), which apparently inhibits collagenase, and is proposed for use in the treatment of cancer, arteriosclerosis and inflammation.



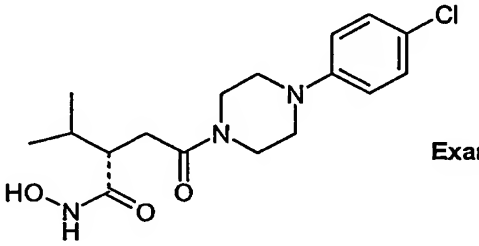
Example 18 (page 15)

Hou et al., 2001, describe the following compound (Q^2 has backbone=2; is alkylene; is α-substituted), which apparently inhibits the proteinase gelatinase-A.



Compound a15 (page 5314)

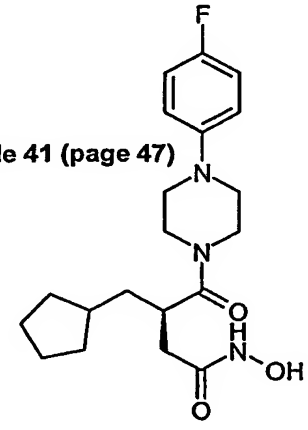
Owen et al., 2001, describe the following compound (Q^2 has backbone=2; is alkylene), which apparently inhibits certain MMPs, and is proposed for use in the treatment of inflammation.



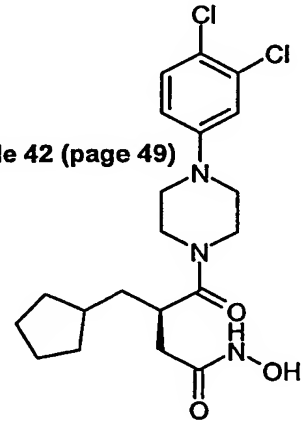
Example 4 (page 20)

Pratt et al., 2001, describe the following compounds (Q^2 has backbone=2; is alkylene), which apparently have anti-bacterial activity.

Example 41 (page 47)



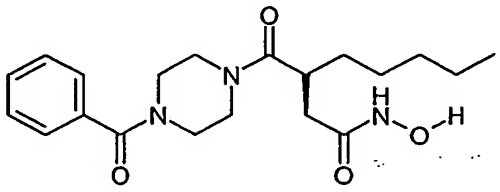
Example 42 (page 49)



Piperazino Bisamides

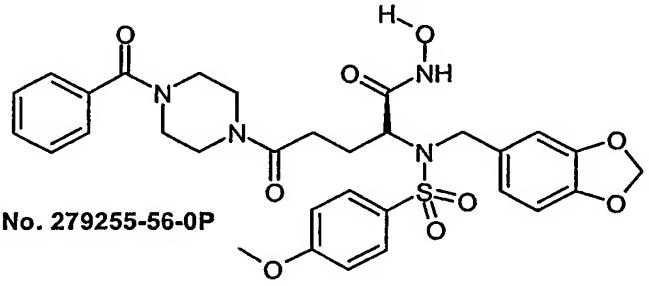
A number of hydroxamic acids comprising a piperazine moiety with carbonyl groups adjacent to each nitrogen atom of the piperazine moiety are known.

Chong et al., 2002 describe the following compound (Q^2 has backbone=2; is alkylene) as an inhibitor of peptide deformylase for use as an antibiotic.

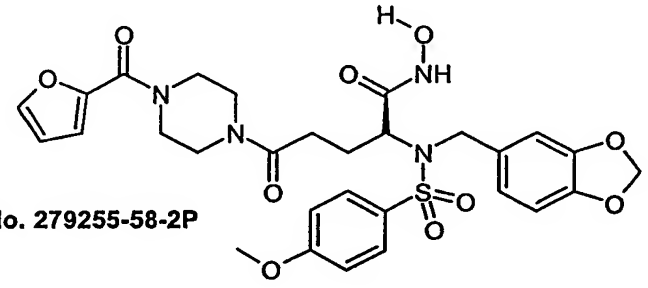


CAS No. 409129-96-0P

Billedeau et al., 2000 describe the following two compounds (Q^2 has backbone=3; is alkylene; is α-substituted) as inhibitors of procollagen C-proteinase for use in the treatment of fibrosis, sclerosis, arthritis and acute respiratory distress syndrome.



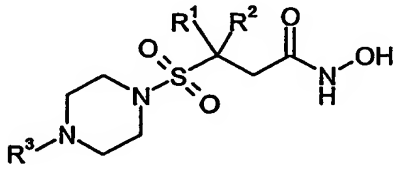
CAS No. 279255-56-0P



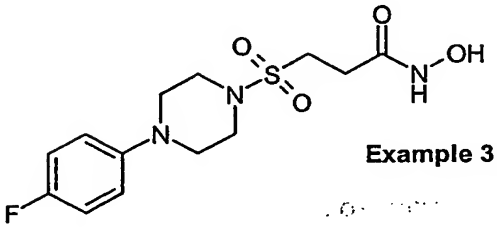
CAS No. 279255-58-2P

Piperazino Sulfonamides

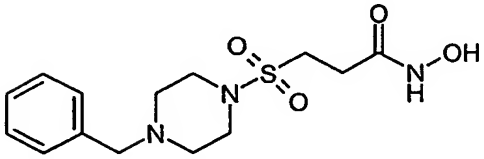
Barlaam et al., 2000, describe compounds of the following type (wherein R^3 may be, e.g., phenyl) (Q^2 has backbone=2; is alkylene; is optionally β-substituted), which apparently inhibit MMP-13.



Two examples of such compounds (Q^2 has backbone=2; is alkylene) include the following.

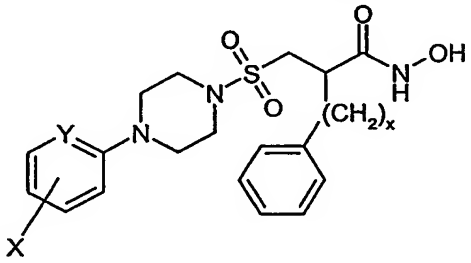


Example 3 (page 29)

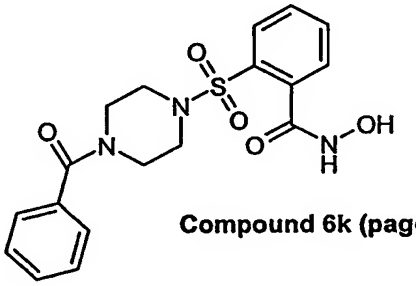


Example 4 (page 31)

Barlaam et al., 2001, describe compounds of the following type (Q^2 has backbone=2; is alkylene) which apparently inhibit MMP-13 and collagenase 3.

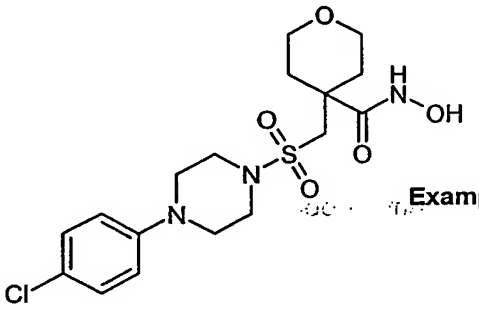


Barta et al., 2000, describe the following compound (Q^2 has backbone=2; is phenylene), which apparently inhibits MMP-2 and MMP-13.



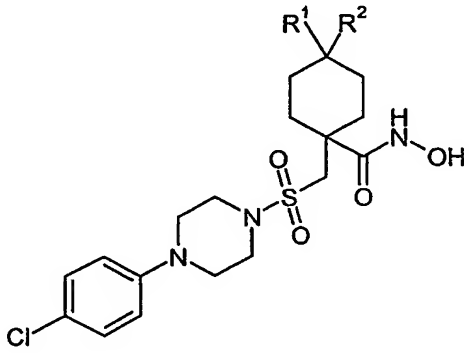
Compound 6k (page 2816)

Baxter et al., 1999, (Darwin Discovery, UK) describe the following compound (Q^2 has backbone=2; is alkylene), which apparently inhibits certain MMPs.

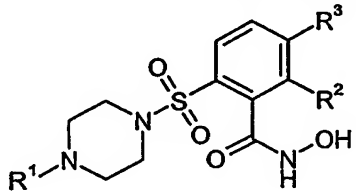


Example 35 (page 29)

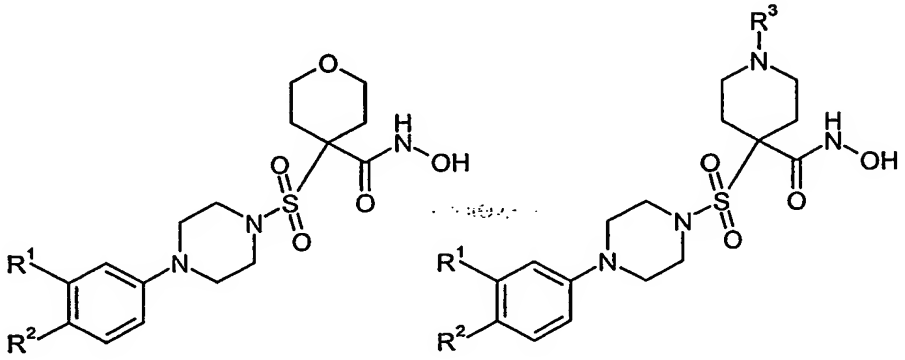
Baxter et al., 2000, (Darwin Discovery, UK) describe compounds of the following type (Q^2 has backbone=2; is alkylene), which apparently inhibitor certain MMPs.



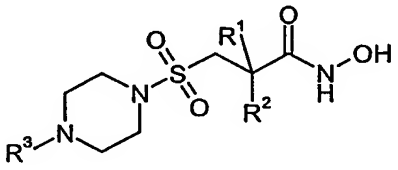
Bedell et al., 2000, and Bedell et al., 2001, describe compounds of the following type (Q^2 has backbone=2; is phenylene), which apparently inhibit certain MMPs.



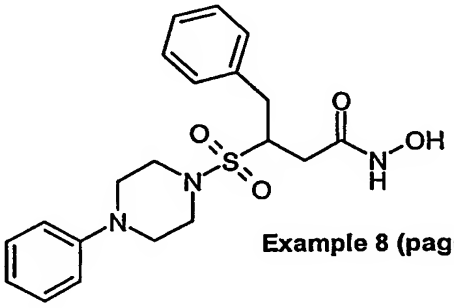
De Crescenzo et al., 2000, describe compounds of the following type (Q^2 has backbone=2; is alkylene), which apparently inhibit certain MMPs.



Hannah et al., 2001, (Darwin Discovery, UK) describe compounds of the following type (Q^2 has backbone=2; is alkylene; is optionally α-substituted), which apparently inhibit certain MMPs.

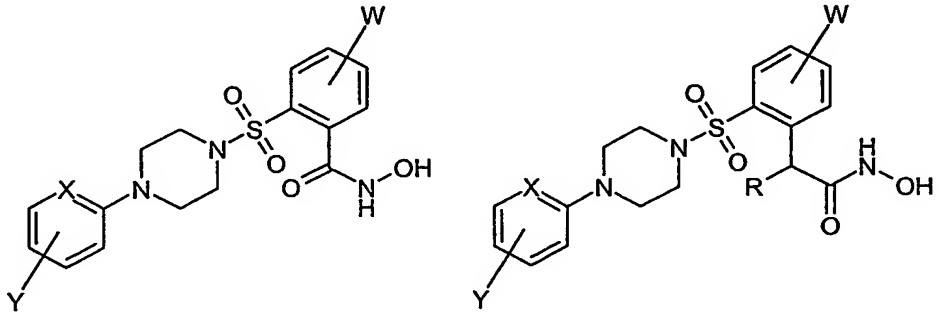


Martin et al., 2000, describes the following compound (Q^2 has backbone=2; is alkylene), which apparently inhibits certain MMPs.

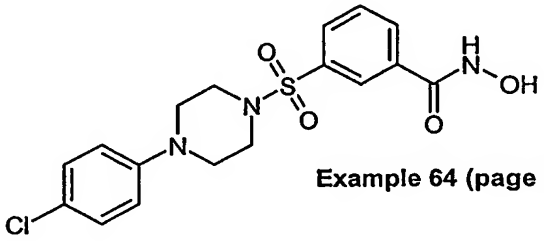


Example 8 (page 23)

Owen et al., 2000, (Darwin Discovery, UK) describe compounds of the following type (Q^2 has backbone=2; is phenylene), which are apparently inhibit certain MMPs.



Owen et al., 2000, (Darwin Discovery, UK) also describes the following compound (Q^2 has backbone=3; is phenylene):



Example 64 (page 32)

SUMMARY OF THE INVENTION

One aspect of the invention pertains to active carbamic acid compounds, as described herein.

Another aspect of the invention pertains to active compounds, as described herein, which inhibit HDAC activity.

Another aspect of the invention pertains to active compounds, as described herein, which treat conditions which are known to be mediated by HDAC, or which are known to be treated by HDAC inhibitors (such as, e.g., trichostatin A).

Another aspect of the invention pertains to active compounds, as described herein, which (a) regulate (e.g., inhibit) cell proliferation; (b) inhibit cell cycle progression; (c) promote apoptosis; or (d) a combination of one or more of these.

Another aspect of the invention pertains to active compounds, as described herein, which are anti-HDAC agents, and which treat a condition mediated by HDAC.

Another aspect of the invention pertains to active compounds, as described herein, which are anticancer agents, and which treat cancer.

Another aspect of the invention pertains to active compounds, as described herein, which are antiproliferative agents, and which treat a proliferative condition.

Another aspect of the invention pertains to active compounds, as described herein, which are antipsoriasis agents, and which treat psoriasis.

Another aspect of the present invention pertains to a composition comprising a compound, as described herein, and a carrier.

Another aspect of the present invention pertains to a composition comprising a compound, as described herein, and a pharmaceutically acceptable carrier.

Another aspect of the present invention pertains to methods of inhibiting HDAC in a cell, comprising contacting said cell with an effective amount of an active compound, as described herein, whether *in vitro* or *in vivo*.

Another aspect of the present invention pertains to methods of (a) regulating (e.g., inhibiting) cell proliferation; (b) inhibiting cell cycle progression; (c) promoting apoptosis; or (d) a combination of one or more of these, comprising contacting a cell with an effective amount of an active compound, as described herein, whether *in vitro* or *in vivo*.

Another aspect of the present invention pertains to methods of treating a condition which is known to be mediated by HDAC, or which is known to be treated by HDAC inhibitors (such as, e.g., trichostatin A), comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to methods of treating cancer, comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to methods of treating a proliferative condition comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to methods of treating psoriasis comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the treatment of a condition mediated by HDAC, a condition known to be treated by HDAC inhibitors (such as, e.g., trichostatin A), cancer, a proliferative condition, psoriasis, or other condition as described herein.

Another aspect of the present invention pertains to a kit comprising (a) the active compound, preferably provided as a pharmaceutical composition and in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the active compound.

Another aspect of the present invention pertains to compounds *obtainable* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to compounds *obtained* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to novel intermediates, as described herein, which are suitable for use in the methods of synthesis described herein.

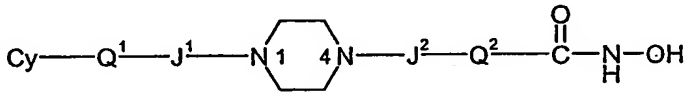
Another aspect of the present invention pertains to the use of such novel intermediates, as described herein, in the methods of synthesis described herein.

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspects of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Compounds

In one aspect, the present invention pertains to carbamic acid compounds of the formula:



(1)

wherein:

Cy is independently a cyclyl group;

Q^1 is independently a covalent bond or cyclyl leader group;

the piperazin-1,4-diyl group is optionally substituted;

J^1 is independently a covalent bond or -C(=O)- ;

J^2 is independently -C(=O)- or $-S(=O)_2-$;

Q^2 is independently an acid leader group;

wherein:

Cy is independently:

C_{3-20}carbocyclyl,

C_{3-20}heterocyclyl, or

C_{5-20}aryl;

and is optionally substituted;

Q^1 is independently:

a covalent bond;

C_{1-7}alkylene; or

C_{1-7}alkylene-X-C_{1-7}alkylene, -X-C_{1-7}alkylene, or C_{1-7}alkylene-X-,

wherein X is -O- or -S-;

and is optionally substituted;

Q^2 is independently:

C_{4-8}alkylene;

and is optionally substituted;

and has a backbone length of at least 4 atoms;

or:

Q^2 is independently:

C_{5-20}arylene;
C_{5-20}arylene-C_{1-7}alkylene;
C_{1-7}alkylene-C_{5-20}arylene; or,
C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene;
and is optionally substituted;
and has a backbone length of at least 4 atoms;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

In preferred embodiments, the carbamic acid group, -C(=O)NHOH, is unmodified (e.g., is not an ester).

Note that each of the groups -J^1-Q^1-Cy and -J^2-Q^2-C(=O)NHOH is a monovalent and monodentate species; and that is it not intended that these groups be linked, other than via the N-1 and N-4 atoms, respectively, of the piperazin-1,4-diyl group.

The Piperazin-1,4-diyl Group

The piperazin-1,4-diyl group is optionally substituted, i.e., unsubstituted or substituted.

In one embodiment, the piperazin-1,4-diyl group is unsubstituted (i.e., unsubstituted at the 2-, 3-, 5-, and 6-positions).

In one embodiment, the piperazin-1,4-diyl group is substituted (i.e., substituted at one or more the 2-, 3-, 5-, and 6-positions.

For example, in one embodiment, the piperazin-1,4-diyl group is substituted (i.e., substituted at one or more the 2-, 3-, 5-, and 6-positions with C_{1-4}alkyl, for example, -Me or -Et.

For example, in one embodiment, the piperazin-1,4-diyl group is: unsubstituted piperazin-1,4-diyl or 2-methyl-piperazin-1,4-diyl.

The piperazin-1,4-diyl group may be in any conformation, including, but not limited to, chair-, boat-, or twist-forms.

The Linkers, J^1 and J^2

In one embodiment, J^1 is independently a covalent bond.

In one embodiment, J^1 is independently -C(=O)-.

In one embodiment, J^2 is independently -C(=O)-.

In one embodiment, J^2 is independently $-S(=O)_2-$.

In one embodiment:

J^1 is a covalent bond and J^2 is -C(=O)-; or:

J^1 is -C(=O)- and J^2 is -C(=O)-; or:

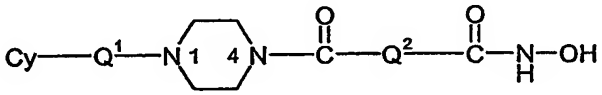
J^1 is a covalent bond and J^2 is $-S(=O)_2-$.

In one embodiment:

J^1 is a covalent bond and J^2 is -C(=O)-; or:

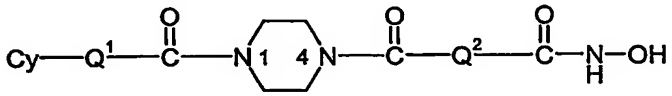
J^1 is -C(=O)- and J^2 is -C(=O)-.

In one embodiment, J^1 is a covalent bond and J^2 is -C(=O)- (and the compounds may be referred to as "piperazino-amides"):



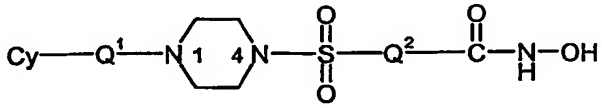
(2)

In one embodiment, J^1 is -C(=O)- and J^2 is -C(=O)- (and the compounds may be referred to as "piperazino-bisamides"):



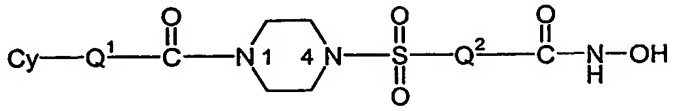
(3)

In one embodiment, J^1 is a covalent bond and J^2 is $-S(=O)_2-$ (and the compounds may be referred to as "piperazino-sulfonamides"):



(4)

In one embodiment, J^1 is -C(=O)- and J^2 is $-S(=O)_2-$ (and the compounds may be referred to as "piperazino-amide-sulfonamides"):



(5)

For the avoidance of doubt, it is intended that, if there is a -C(=O)- group immediately adjacent to the N-1 atom of the piperazin-1-4-diyl group, then that -C(=O)- group must be assigned as J^1 (that is, J^1 is -(C=O)-) and not as part of Q^1 (e.g., as part of an oxo-substituted Q^1 group). For example, if the Cy-Q^1-J^1- group is Ph-CH_2-C(=O)-, then Cy is Ph-, Q^1 is $-CH_2-$, and J^1 is -C(=O)-.

Assigning the Cyclyl Group, Cy

If, within the group -J^1-Q^1-Cy, there is a plurality of candidate groups satisfying the definition of Cy (referred to as candidate Cy groups), then the candidate Cy group which is furthest from from the N-1 atom of the piperazin-1,4-diyl group is identified as Cy (and referred to as "the relevant Cy group").

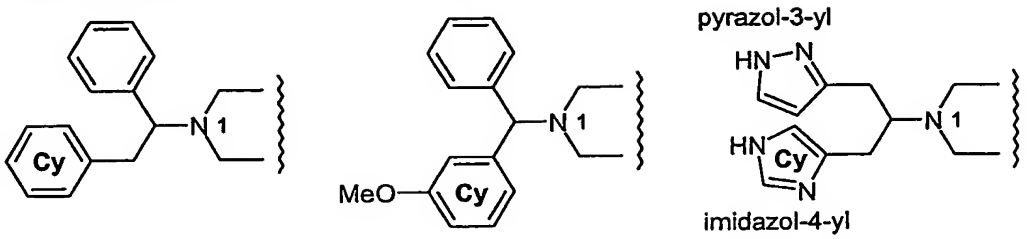
In this context, distance (e.g., further, furthest) is measured as the number of chain atoms in the shortest continuous chain linking the groups (i.e., the N-1 atom and Cy).

If there is a plurality of furthest candidate Cy groups, then the one (including any substituents) with the largest molecular weight is the relevant one.

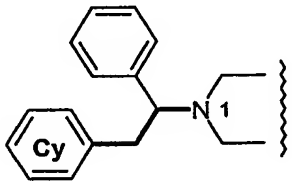
If there is a plurality of furthest heaviest candidate Cy groups, then the one (excluding any substituents) with the most annular heteroatoms is the relevant one.

If there is a plurality of furthest heaviest candidate Cy groups with the most annular heteroatoms, then the one with an IUPAC name which alphabetically precedes the other(s), is the relevant one.

Some illustrative examples are shown below.



If the group, Q^1, is a cyclyl leader group (i.e., not a covalent bond) and/or J1 is -C(=O)-, the group $-Q^1-J^1-$ has a backbone length, as determined by the number of chain atoms in the shortest continuous chain of atoms linking the relevant cyclyl group, Cy, and the N-1 atom of the piperazin-1,4-diyl group. In the following example, $-Q^1-J^1-$ has a backbone length of 2.



The Cyclyl Group, Cy

Cy is independently: C_{3-20}carbocyclyl, C_{3-20}heterocyclyl, or C_{5-20}aryl; and is optionally substituted.

In one embodiment, Cy is independently C_{3-20}carbocyclyl; and is optionally substituted.

In one embodiment, Cy is independently monocyclic C_{3-7}carbocyclyl, and is optionally substituted.

In one embodiment, Cy is independently monocyclic C_{5-6}carbocyclyl, and is optionally substituted.

In one embodiment, Cy is independently C_{3-20}carbocyclyl derived from one of the following: cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclopentene, cyclohexene, norbornane, adamantane, cyclopentanone, and cyclohexanone; and is optionally substituted.

In one embodiment, Cy is independently C_{3-20}heterocyclyl; and is optionally substituted.

In one embodiment, Cy is independently monocyclic C_{3-7}heterocyclyl, and is optionally substituted.

In one embodiment, Cy is independently monocyclic C_{5-6}heterocyclyl, and is optionally substituted.

In one embodiment, Cy is independently C_{3-20}heterocyclyl derived from one of the following: piperidine, azepine, tetrahydropyran, morpholine, azetidine, piperazine, imidazoline, piperazinedione, and oxazolinone; and is optionally substituted.

In one embodiment, Cy is independently C_{5-20}aryl; and is optionally substituted.

In one embodiment, Cy is independently C_{5-20}carboaryl or C_{5-20}heteroaryl; and is optionally substituted.

In one embodiment, Cy is independently C_{5-20}heteroaryl; and is optionally substituted. In one embodiment, Cy is monocyclic C_{5-20}heteroaryl; and is optionally substituted. In one embodiment, Cy is monocyclic C_{5-6}heteroaryl; and is optionally substituted.

In one embodiment, Cy is independently C_{5-20}carboaryl; and is optionally substituted. In one embodiment, Cy is monocyclic C_{5-20}carboaryl; and is optionally substituted. In one embodiment, Cy is monocyclic C_{5-6}carboaryl; and is optionally substituted. In one embodiment, Cy is phenyl; and is optionally substituted.

In one embodiment, Cy is independently C_{5-20}aryl derived from one of the following: benzene, pyridine, furan, indole, pyrrole, imidazole, pyrimidine, pyrazine, pyridizine, naphthalene, quinoline, indole, benzimidazole, benzothiofuran, fluorene, acridine, and carbazole; and is optionally substituted.

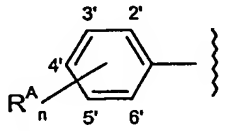
Examples of substituents on Cy include, but are not limited to, those described under the heading "Substituents" below.

In one embodiment, the optional substituents on Cy are as defined under the heading "The Cyclyl Group, Cy: Optionally Substituted Phenyl: Substituents."

The Cyclyl Group, Cy: Optionally Substituted Phenyl

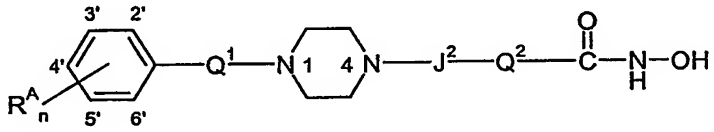
In one embodiment, Cy is independently an optionally substituted phenyl group.

In one embodiment, Cy is independently an optionally substituted phenyl group of the formula:



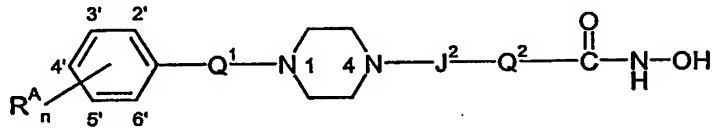
wherein n is independently an integer from 0 to 5, and each R^A is independently a substituent as defined herein.

In one embodiment, Cy is an optionally substituted phenyl group, Q^1 is a covalent bond or a cyclyl leader group, J^1 is a covalent bond, and the compounds have the following formula:



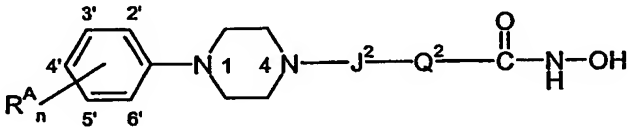
(6)

In one embodiment, Cy is an optionally substituted phenyl group, Q^1 is a cyclyl leader group, J^1 is a covalent bond, and the compounds have the following formula:



(7)

In one embodiment, Cy is an optionally substituted phenyl group, Q^1 is a covalent bond, J^1 is a covalent bond, and the compounds have the following formula:



(8)

In one embodiment, n is an integer from 0 to 5.

In one embodiment, n is an integer from 0 to 4.

In one embodiment, n is an integer from 0 to 3.

In one embodiment, n is an integer from 0 to 2.

In one embodiment, n is 0 or 1.

In one embodiment, n is an integer from 1 to 5.

In one embodiment, n is an integer from 1 to 4.

In one embodiment, n is an integer from 1 to 3.

In one embodiment, n is 1 or 2.

In one embodiment, n is 5.

In one embodiment, n is 4.

In one embodiment, n is 3.

In one embodiment, n is 2.

In one embodiment, n is 1.

In one embodiment, n is 0.

If the phenyl group has less than the full complement of ring substituents, R^A, they may be arranged in any combination. For example, if n is 1, R^A may be in the 2'-, 3'-, 4'-, 5'-, or 6'-position. Similarly, if n is 2, the two R^A groups may be in, for example, the 2',3'-, 2',4'-, 2',5'-, 2',6'-, 3',4'-, or 3',5'-positions. If n is 3, the three R^A groups may be in, for example, the 2',3',4'-, 2',3',5'-, 2',3',6'-, or 3',4',5'-positions.

In one embodiment, n is 0.

In one embodiment, n is 1, and the R^A group is in the 4'-position.

In one embodiment, n is 2, and one R^A group is in the 4'-position, and the other R^A group is in the 2'-position.

In one embodiment, n is 2, and one R^A group is in the 4'-position, and the other R^A group is in the 3'-position.

<u>The Cyclyl Group, Cy: Optionally Substituted Phenyl: Substituents</u>

Examples of substituents on Cy (e.g., R^A), include, but are not limited to, those described under the heading "Substituents" below.

Further examples of substituents on Cy (e.g., R^A), include, but are not limited to, those described below.

In one embodiment, each of the substituents on Cy (e.g., each R^A), is independently selected from:

(1) ester;

(2) amido;

(3) acyl;

(4) halo;

(5) hydroxy;

(6) ether;

(7) C_{1-7}alkyl, including substituted C_{1-7}alkyl;

(8) C_{5-20}aryl, including substituted C_{5-20}aryl;

(9) sulfonyl;

(10) sulfonamido;

(11) amino;

(12) morpholino;

(13) nitro;

(14) cyano.

In one embodiment, each of the substituents on Cy (e.g., each R^A), is independently selected from:

(1) -C(=O)OR^1, wherein R^1 is independently C_{1-7}alkyl as defined in (7);

(2) -C(=O)NR^2R^3, wherein each of R^2 and R^3 is independently -H or C_{1-7}alkyl as defined in (7);

(3) -C(=O)R^4, wherein R^4 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(4) -F, -Cl, -Br, -I;

(5) -OH;

(6) -OR^5, wherein R^5 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(7) C_{1-7}alkyl, including substituted C_{1-7}alkyl, e.g.,

halo-C_{1-7}alkyl;

amino-C_{1-7}alkyl (e.g., -$(CH_2)_w$-amino);

carboxy-C_{1-7}alkyl (e.g., -$(CH_2)_w$-COOH);

hydroxy-C_{1-7}alkyl (e.g., -$(CH_2)_w$-OH);

C_{1-7}alkoxy-C_{1-7}alkyl (e.g., -$(CH_2)_w$-O-C_{1-7}alkyl);

C_{5-20}aryl-C_{1-7}alkyl;

wherein w is 1, 2, 3, or 4;

(8) C_{5-20}aryl, including substituted C_{5-20}aryl;

(9) $-SO_2R^7$, wherein R^7 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(10) $-SO_2NR^8R^9$, wherein each of R^8 and R^9 is independently -H or C_{1-7}alkyl as defined in (7);

(11) $-NR^{10}R^{11}$, wherein each of R^{10} and R^{11} is indenpendently –H or C_{1-7} alkyl as defined in (7);

(12) morpholino;

(13) nitro;

(14) cyano.

In one embodiment, each of the substituents on Cy (e.g., each R^A), is independently selected from:

(1) -C(=O)OMe, -C(=O)OEt, -C(=O)O(Pr), -C(=O)O(iPr), -C(=O)O(nBu), -C(=O)O(sBu), -C(=O)O(iBu), -C(=O)O(tBu), -C(=O)O(nPe);

$-C(=O)OCH_2CH_2OH$, $-C(=O)OCH_2CH_2OMe$, $-C(=O)OCH_2CH_2OEt$;

(2) $-(C=O)NH_2$, $-(C=O)NMe_2$, $-(C=O)NEt_2$, $-(C=O)N(iPr)_2$, $-(C=O)N(CH_2CH_2OH)_2$;

(3) -(C=O)Me, -(C=O)Et, -(C=O)-cHex, -(C=O)Ph;

(4) -F, -Cl, -Br, -I;

(5) -OH;

(6) -OMe, -OEt, -O(iPr), -O(tBu), -OPh;

$-OCF_3$, $-OCH_2CF_3$;

$-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, $-OCH_2CH_2OEt$;

$-OCH_2CH_2NH_2$, $-OCH_2CH_2NMe_2$, $-OCH_2CH_2N(iPr)_2$;

-OPh, -OPh-Me, -OPh-OH, -OPh-OMe, O-Ph-F, -OPh-Cl, -OPh-Br, -OPh-I;

(7) -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, -tBu, -nPe;

$-CF_3$, $-CH_2CF_3$;

$-CH_2CH_2OH$, $-CH_2CH_2OMe$, $-CH_2CH_2OEt$;

$-CH_2CH_2NH_2$, $-CH_2CH_2NMe_2$, $-CH_2CH_2N(iPr)_2$;

$-CH_2$-Ph;

(8) -Ph, -Ph-Me, -Ph-OH, -Ph-OMe, -Ph-F, -Ph-Cl, -Ph-Br, -Ph-I;

(9) $-SO_2Me$, $-SO_2Et$, $-SO_2Ph$;

(10) $-SO_2NH_2$, $-SO_2NMe_2$, $-SO_2NEt_2$;

(11) $-NMe_2$, $-NEt_2$;

(12) morpholino;

(13) $-NO_2$;

(14) -CN.

In one embodiment, each of the substituents on Cy (e.g., each R^A), is independently selected from:

-C(=O)OMe, -C(=O)O(Pr), -C(=O)NHMe, -C(=O)Et, C(=O)Ph,
$-OCH_2CH_2OH$, -OMe, -OPh,
-nPr, iPr, $-CF_3$, $-CH_2CH_2OH$, $-CH_2CH_2NMe_2$,
-Ph, -Ph-F, -Ph-Cl,
$-SO_2Me$, $-SO_2Me_2$, $-NMe_2$,
-F, -Cl, -Me, -Et, -OMe, -OEt, $-CH_2$-Ph, -O-CH_2-Ph.

In one embodiment, each of the substituents on Cy (e.g., each R^A), is independently selected from:

-F, -Cl, -Me, -Et, -OMe, -OEt, -Ph, -OPh, $-CH_2$-Ph, -O-CH_2-Ph.

Examples of some preferred substituents on Cy (e.g., R^A), include, but are not limited to, the following: fluoro, chloro, bromo, iodo, methyl, ethyl, isopropyl, t-butyl, cyano, trifluoromethyl, hydroxy, methoxy, ethoxy, isopropoxy, trifluoromethoxy, phenoxy, methylthio, trifluoromethylthio, hydroxymethyl, amino, dimethylamino, diethylamino, morpholino, amido (unsubstituted, i.e., $-CONH_2$), acetamido, acetyl, nitro, sulfonamido (unsubstituted, i.e., $-SO_2NH_2$), and phenyl.

The Cyclyl Leader Group, Q^1

In one embodiment, Q^1 is independently:
a covalent bond; or
a cyclyl leader group;
and is optionally substituted.

In one embodiment, Q^1 is independently:
a covalent bond.

In one embodiment, Q^1 is independently:
a cyclyl leader group;
and is optionally substituted.

In one embodiment, Q^1 is independently:

a covalent bond;

C_{1-7}alkylene; or

C_{1-7}alkylene-X-C_{1-7}alkylene, -X-C_{1-7}alkylene, or C_{1-7}alkylene-X-;

wherein X is -O- or -S-;

and is optionally substituted.

In one embodiment, Q^1 is independently:

a covalent bond; or

a C_{1-7}alkylene group;

and is optionally substituted.

In one embodiment, Q^1 is independently:

a C_{1-7}alkylene group;

and is optionally substituted.

In one embodiment, Q^1 is independently:

C_{1-7}alkylene-X-C_{1-7}alkylene, -X-C_{1-7}alkylene, or C_{1-7}alkylene-X-;

wherein X is -O- or -S-;

and is optionally substituted.

In one embodiment, in the above alkylene groups, each alkylene group is independently:

(a) a saturated C_{1-7}alkylene group; or:

(b) a partially unsaturated C_{2-7}alkylene group; or:

(c) an aliphatic C_{1-7}alkylene group; or:

(d) a linear C_{1-7}alkylene group; or:

(e) a branched C_{2-7}alkylene group; or:

(f) a saturated aliphatic C_{1-7}alkylene group; or:

(g) a saturated linear C_{1-7}alkylene group; or:

(h) a saturated branched C_{2-7}alkylene group; or:

(i) a partially unsaturated aliphatic C_{2-7}alkylene group; or:

(j) a partially unsaturated linear C_{2-7}alkylene group; or:

(k) a partially unsaturated branched C_{2-7}alkylene group;

and is optionally substituted.

In one embodiment, the above alkylene groups have a maximum number of carbon atoms of 4, e.g., C_{1-4}alkylene, C_{2-4}alkylene.

In one embodiment, the above alkylene groups have a maximum number of carbon atoms of 3, e.g., C_{1-3}alkylene, C_{2-3}alkylene.

In one embodiment, Q^1 is selected so that the N-1 atom of the piperazin-1,4-diyl group is not connected to a carbon atom which is connected to another carbon atom via a non-aromatic carbon-carbon double bond (i.e., C=C). That is, the N-1 atom of the piperazin-1,4-diyl group is not adjacent to a non-aromatic carbon-carbon double bond (i.e., C=C). In this way, groups such as -CH=CH- and -CH_2-CH=CH- are excluded from Q^1, but groups such as -CH=CH-CH_2- are not. Additional embodiments include other embodiments described herein (e.g., those described above) further limited by this restriction upon Q^1.

The Cyclyl Leader Group, Q^1: Covalent Bond

In one embodiment:

Q^1 is independently a covalent bond;

J^1 is independently a covalent bond;

J^2 is independently -C(=O)-.

In one embodiment:

Q^1 is independently a covalent bond;

J^1 is independently -C(=O)-;

J^2 is independently -C(=O)-.

In one embodiment:

Q^1 is independently a covalent bond;

J^1 is independently a covalent bond;

J^2 is independently -$S(=O)_2$-.

In one embodiment:

Q^1 is independently a covalent bond;

J^1 is independently -C(=O)-;

J^2 is independently -$S(=O)_2$-.

The Cyclyl Leader Group, Q^1: Backbone Length

The group $-J^1-Q^1-$ has a backbone length, as determined by the number of chain atoms in the shortest continuous chain of atoms linking the relevant Cy group and the N-1 atom of the piperazin-1,4-diyl group.

In one embodiment, the group $-J^1-Q^1-$ has a backbone of:
from 1 to 7 atoms;
from 1 to 6 atoms;
from 1 to 5 atoms;
from 1 to 4 atoms; or,
from 1 to 3 atoms.

In one embodiment, the group $-J^1-Q^1-$ has a backbone of at least 2 atoms. In this way, groups such as methylene ($-CH_2-$) and substituted methylene ($-CR_2-$ and -CHR-) are excluded.

In one embodiment, the group $-J^1-Q^1-$ has a backbone of at least 3 atoms.
In one embodiment, the group $-J^1-Q^1-$ has a backbone of at least 4 atoms.
In one embodiment, the group $-J^1-Q^1-$ has a backbone of at least 5 atoms.

In one embodiment, the group $-J^1-Q^1-$ has a backbone of:
from 2 to 7 atoms;
from 2 to 6 atoms; or,
from 2 to 5 atoms.

In one embodiment, the group $-J^1-Q^1-$ has a backbone of:
from 3 to 7 atoms;
from 3 to 6 atoms; or,
from 3 to 5 atoms.

In one embodiment, the group $-J^1-Q^1-$ has a backbone of:
from 4 to 7 atoms;
from 4 to 6 atoms; or,
from 4 to 5 atoms.

In one embodiment, the group $-J^1-Q^1-$ has a backbone of 1 atom.
In one embodiment, the group $-J^1-Q^1-$ has a backbone of 2 atoms.
In one embodiment, the group $-J^1-Q^1-$ has a backbone of 3 atoms.
In one embodiment, the group $-J^1-Q^1-$ has a backbone of 4 atoms.
In one embodiment, the group $-J^1-Q^1-$ has a backbone of 5 atoms.

In one embodiment, the backbone of "atoms" is a backbone of "carbon atoms."

Note that, for embodiments which are characterised by, or further characterised by, a backbone length limitation, corresponding changes in the description of that embodiment may be implicit. For example, for an embodiment wherein (a) Q^1 is a partially unsaturated C_{2-7}alkylene group and (b) Q^1 has a backbone of 4 carbon atoms, the term "C_{2-7}alkylene" group is necessarily, and implicitly, interpreted as "C_{4-7}alkylene."

The Cyclyl Leader Group, Q^1: Substituents

In one embodiment, Q^1, if other than a covalent bond, is unsubstituted.
In one embodiment, Q^1, if other than a covalent bond, is optionally substituted.
In one embodiment, Q^1, if other than a covalent bond, is substituted.

Examples of substituents on Q^1 include, but are not limited to, those described under the heading "Substituents" below.

In one embodiment, substituents on Q^1, if present, are as defined under the heading "The Cyclyl Group, Cy: Optionally Substituted Phenyl: Substituents."

In one embodiment, substituents on Q^1, if present, are independently: halo, hydroxy, ether (e.g., C_{1-7}alkoxy), C_{5-20}aryl, acyl, amino, amido, acylamido, or oxo.

In one embodiment, substituents on Q^1, if present, are independently: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -OPr, -Ph, $-NH_2$, $-CONH_2$, or =O.

In one embodiment, substituents on Q^1, if present, are independently -OH or -Ph.

In one embodiment, substituents on Q^1, if present, are independently -Ph.

For example, in one embodiment, Q^1 is unsubstituted methylene, and is $-CH_2-$; in one embodiment, Q^1 phenyl (-Ph) substituted methylene, and is -CH(Ph)-.

For example, in one embodiment, Q^1 is unsubstituted ethylene, and is $-CH_2-CH_2-$; in one embodiment, Q^1 is oxo (=O) substituted ethylene, and is $-C(=O)-CH_2-$; in one embodiment, Q^1 is hydroxy (-OH) substituted ethylene, and is $-CH(OH)-CH_2-$; in one embodiment, Q^1 is phenyl (-Ph) substituted ethylene, and is $-CH_2CH(Ph)-$.

Again, for the avoidance of doubt, it is intended that, if there is a -C(=O)- group immediately adjacent to the N-1 atom of the piperazin-1-4-diyl group, then that -C(=O)- group must be assigned as J^1 (that is, J^1 is -(C=O)-) and not as part of Q^1 (e.g., as part of an oxo-substituted Q^1 group). For example, if the $Cy-Q^1-J^1-$ group is $Ph-CH_2-C(=O)-$, then Cy is Ph-, Q^1 is $-CH_2-$, and J^1 is -C(=O)-.

The Cyclyl Leader Group, Q^1: Alkylene: Certain Embodiments

Note that, for embodiments excluding, e.g., a covalent bond, certain backbone lengths, absence of adjacent carbon-carbon double bonds, etc., it is to be understood that the corresponding species listed below are similarly excluded from the respective embodiments discussed below.

In one embodiment, Q^1 is independently selected from the following:

a covalent bond;

$-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$;

$-CH(CH_3)-$;
$-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2CH(CH_3)-$, $-CH(CH_3)CH_2CH_2CH_2CH(CH_3)-$;

-CH(CH_2CH_3)-;

-CH(CH_2CH_3)CH_2-, -CH_2CH(CH_2CH_3)-;

-CH(CH_2CH_3)CH_2CH_2-, -CH_2CH(CH_2CH_3)CH_2-, -CH_2CH_2CH(CH_2CH_3)-;

-CH(CH_2CH_3)$CH_2CH_2CH_2$-, -CH_2CH(CH_2CH_3)CH_2CH_2-, -CH_2CH_2CH(CH_2CH_3)CH_2-, -$CH_2CH_2CH_2$CH(CH_2CH_3)-;

-CH(CH_2CH_3)$CH_2CH_2CH_2CH_2$-, -CH_2CH(CH_2CH_3)$CH_2CH_2CH_2$-, -CH_2CH_2CH(CH_2CH_3)CH_2CH_2-, -$CH_2CH_2CH_2$CH(CH_2CH_3)CH_2-, -$CH_2CH_2CH_2CH_2$CH(CH_2CH_3)-;

-CH=CH-;

-CH=CHCH_2-, -CH_2CH=CH-;

-CH=CHCH_2CH_2-, -CH_2CH=CHCH_2-, -CH_2CH_2CH=CH-;

-CH=C$HCH_2CH_2CH_2$-, -CH_2CH=CHCH_2CH_2-, -CH_2CH_2CH=CHCH_2-, -$CH_2CH_2CH_2$CH=CH-;

-CH=C$HCH_2CH_2CH_2CH_2$-, -CH_2CH=C$HCH_2CH_2CH_2$-, -CH_2CH_2CH=CHCH_2CH_2-, -$CH_2CH_2CH_2$CH=CHCH_2-, -$CH_2CH_2CH_2CH_2$CH=CH-;

-C(CH_3)=CH-, -CH=C(CH_3)-;

-C(CH_3)=CHCH_2-, -CH=C(CH_3)CH_2-, -CH=CHCH(CH_3)-;

-CH(CH_3)CH=CH-, -CH_2C(CH_3)=CH-, -CH_2CH=C(CH_3)-;

-CH=CHCH=CH-;

-CH=CHCH=CHCH_2-, -CH_2CH=CHCH=CH-, -CH=CHCH_2CH=CH-;

-CH=CHCH=CHCH_2CH_2-, -CH=CHCH=CHCH=CH_2-, -CH=CHCH_2CH_2CH=CH-, -CH_2CH=CHCH=CHCH_2-, -CH_2CH=CHCH_2CH=CH-, -CH_2CH_2CH=CHCH=CH-;

-C(CH_3)=CHCH=CH-, -CH=C(CH_3)CH=CH-, -CH=CHC(CH_3)=CH-, -CH=CHCH=C(CH_3)-;

-C≡C-;

-C≡CCH_2-, -CH_2C≡C-; -C≡CCH(CH_3)-, -CH(CH_3)C≡C-;

-C≡CCH_2CH_2-, -CH_2C≡CCH_2-, -CH_2CH_2C≡C-;

-C≡CCH(CH_3)CH_2-, -C≡CCH_2CH(CH_3)-;

-CH(CH_3)C≡CCH_2-, -CH_2C≡CCH(CH_3)-;

-CH(CH_3)CH_2C≡C-, -CH_2CH(CH_3)C≡C-;

-C≡CCH=CH-, -CH=CHC≡C-, -C≡CC≡C-;

-C≡CCH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$C≡C-;

-C≡CCH$_2$CH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$CH$_2$C≡C-;

-C≡CCH=CHCH=CH-, -CH=CHC≡C-CH=CH-, -CH=CHCH=CHC≡C-;

-C(CH$_3$)=CHC≡C-, -CH=C(CH$_3$)C≡C-, -C≡CC(CH$_3$)=CH-, -C≡CCH=C(CH$_3$)-.

In one embodiment, Q^1 is selected from:

a covalent bond;

-CH$_2$-, -(CH$_2$)$_2$-, -(CH$_2$)$_3$-, -(CH$_2$)$_4$-, -(CH$_2$)$_5$-, -(CH$_2$)$_6$-;

-CH(CH$_3$)CH$_2$CH$_2$CH$_2$CH$_2$-, -CH$_2$CH(CH$_3$)CH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$CH(CH$_3$)CH$_2$-, -CH$_2$CH$_2$CH$_2$CH$_2$CH(CH$_3$)-;

-CH=CH-;

-CH=CHCH$_2$-, -CH=C(Me)CH$_2$-;

-CH=CH-CH=CH-;

-CH=CH-CH=CHCH$_2$-, -CH=CHCH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$CH=CH-;

-CH=CHCH$_2$CH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$CH$_2$CH=CH-;

-C(CH$_3$)=CHCH=CH-, -CH=C(CH$_3$)CH=CH-, -CH=CHC(CH$_3$)=CH-, -CH=CHCH=C(CH$_3$)-;

In one embodiment, Q^1 is selected from:

a covalent bond;

-CH$_2$-, -(CH$_2$)$_2$-, -(CH$_2$)$_3$-, -(CH$_2$)$_4$-, -(CH$_2$)$_5$-,

-CH=CH-;

-CH=CHCH$_2$-, -CH=C(Me)CH$_2$-;

-CH=CH-CH=CH-;

-C(CH$_3$)=CHCH=CH-, -CH=C(CH$_3$)CH=CH-, -CH=CHC(CH$_3$)=CH-, -CH=CHCH=C(CH$_3$)-;

-CH=CHCH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$CH=CH-.

In one embodiment, Q^1 is independently selected from:

a covalent bond;

-CH$_2$-, -(CH$_2$)$_2$-, -(CH$_2$)$_3$-, -(CH$_2$)$_4$-, -(CH$_2$)$_5$-;

-CH=CHCH$_2$-;

-CH=C(Me)CH$_2$-; and,

-CH=CH-CH=CHCH$_2$-.

In one embodiment, Q^1 is independently selected from:

a covalent bond;

$-CH_2-$;

$-CH_2CH_2-$;

$-CH_2CH_2CH_2-$;

$-CH=CHCH_2-$;

$-CH=C(Me)CH_2-$; and,

$-CH=CH-CH=CHCH_2-$.

In one embodiment, Q^1 is independently selected from:

a covalent bond;

$-CH_2-$;

-CH(*Ph)-;

$-CH_2CH_2-$;

$-CH(*Ph)CH_2-$;

$-CH_2CH(*Ph)-$;

$-CH_2CH_2CH_2-$;

$-CH=CHCH_2-$;

$-CH=C(Me)CH_2-$; and,

$-CH=CH-CH=CHCH_2-$;

wherein * indicates that the group (e.g., Ph) is optionally substituted with one or more substituents as defined above under the heading "The Cyclyl Group, Cy: Optionally Substituted Phenyl: Substituents."

The Cyclyl Leader Group, Q^1: Ethers and Thioethers: Certain Embodiments

Note that, for embodiments excluding, e.g., a covalent bond, certain backbone lengths, absence of adjacent carbon-carbon double bonds, etc., it is to be understood that the corresponding species listed below are similarly excluded from the respective embodiments discussed below.

In one embodiment, Q^1 is independently selected from the following:

$-(CH_2)_a-X-(CH_2)_b-$

wherein X is -O- or -S- and

a and b are each independently 1, 2, 3, 4, 5, 6, or 7;
and a+b is at least 1.

In one embodiment, Q^1 is independently selected from the following:

$-O-(CH_2)_a-$
$-S-(CH_2)_a-$
$-(CH_2)_a-O-$
$-(CH_2)_a-S-$
$-(CH_2)_a-O-(CH_2)_b-$
$-(CH_2)_a-S-(CH_2)_b-$
wherein a and b are each independently 1, 2, 3, 4, 5, 6, or 7.

In one embodiment, Q^1 is independently selected from the following:

$-O-CH_2-$; $-O-CH_2CH_2-$; $-O-CH_2CH_2CH_2-$;
$-S-CH_2-$; $-S-CH_2CH_2-$; $-S-CH_2CH_2CH_2-$;

$-CH_2-O-$; $-CH_2CH_2-O-$; $-CH_2CH_2CH_2-O-$;
$-CH_2-S-$; $-CH_2CH_2-S-$; $-CH_2CH_2CH_2-S-$;

$-CH_2-O-CH_2-$; $-CH_2-O-CH_2CH_2-$; $-CH_2CH_2-O-CH_2-$; and
$-CH_2CH_2-O-CH_2CH_2-$.

<u>The Group $-Q^1-J^1-$: Certain Embodiments</u>

In one embodiment, the group $-Q^1-J^1-$ has a formula selected from:

$-CH_2-$;
$-CH(*Ph)-$;
$-CH_2CH_2-$;
$-CH_2CH(*Ph)-$;
$-CH(*Ph)CH_2-$;
$-CH_2CH_2CH_2-$;

$-C(=O)-$;
$-CH_2-C(=O)-$;
$-CH(*Ph)-C(=O)-$;

$-CH_2CH_2-C(=O)-$;

$-O-CH_2-$;
$-O-CH_2CH_2-$;
$-CH_2-O-$;
$-CH_2CH_2-O-$; and,

$-O-CH_2-C(=O)-$.

wherein * indicates that the group (e.g., Ph) is optionally substituted with one or more substituents as defined above under the heading "The Cyclyl Group, Cy: Optionally Substituted Phenyl: Substituents."

The Group Cy-Q^1-: Certain Embodiments

In one embodiment, the group Cy-Q^1- has a formula selected from:

*Ph-;
*Ph-CH_2-;
$(*Ph)_2CH$-;
*Ph-CH_2CH_2-;
$(*Ph)_2$-CH_2CH_2-;
*Ph-$CH_2CH(*Ph)$-;
*Ph-$CH_2CH_2CH_2$-;
*Ph-$CH=CHCH_2$-;
*Ph-$CH=C(Me)CH_2$-;
*Ph-$CH=CHCH=CHCH_2$-;
(*pyrid-3-yl)-$CH=CHCH_2$-; and,
(*cyclohexyl)-CH_2CH_2-;

wherein * indicates that the group (e.g., Ph, pyrid-3-yl, cyclohexyl) is optionally substituted with one or more substituents as defined above under the heading "The Cyclyl Group, Cy: Optionally Substituted Phenyl: Substituents."

In one embodiment, * indicates that the group (e.g., Ph, pyrid-3-yl, cyclohexyl) is optionally substituted with one or more of: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -OPr, -Ph, $-NH_2$, and $-CONH_2$.

The Acid Leader Group, Q^2

The acid leader group, Q^2, is independently:

C_{4-8}alkylene;
and is optionally substituted;
and has a backbone length of at least 4 atoms;

or: C_{5-20}arylene;
C_{5-20}arylene-C_{1-7}alkylene;
C_{1-7}alkylene-C_{5-20}arylene; or,
C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene;
and is optionally substituted;
and has a backbone length of at least 4 atoms.

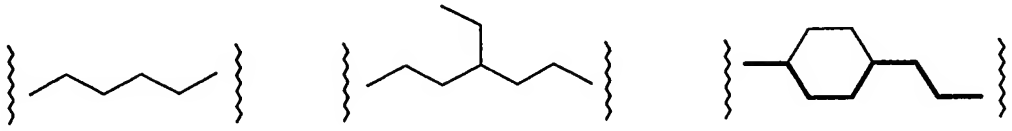
In one embodiment, the acid leader group, Q^2, is independently:
C_{4-8}alkylene;
and is optionally substituted;
and has a backbone length of at least 4 atoms.

In one embodiment, the acid leader group, Q^2, is independently:
C_{5-20}arylene;
C_{5-20}arylene-C_{1-7}alkylene;
C_{1-7}alkylene-C_{5-20}arylene;
C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene; or,
and is optionally substituted;
and has a backbone length of at least 4 atoms.

The Acid Leader Group, Q^2: Backbone Length

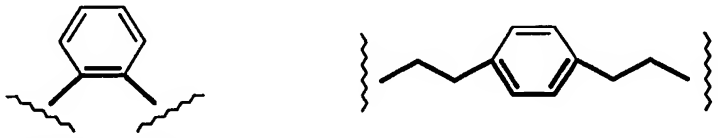
The acid leader group, Q^2, has a backbone length, as determined by the number of chain atoms in the shortest continuous chain of atoms linking the N-4 atom of the piperazin-1,4-diyl group and the carbamic acid group, -C(=O)NHOH.

If Q^2 is alkylene, Q^2 necessarily has a backbone of at least 1 atom. Some examples are shown below.



backbone length = 4 backbone length = 5 backbone length = 6

If Q^2 is arylene, arylene-alkylene, alkylene-arylene, alkylene-arylene-alkylene, Q^2 necessarily has a backbone of at least 2 atoms. Some examples are shown below.



backbone length = 2 backbone length = 8

Without wishing to be bound to any particular theory, it is believed that Q^2 groups with shorter backbone lengths prevent or reduce the interaction of the carbamic acid group (-C(=O)NHOH) with HDAC (or its complexes), and thereby reduce the compound's activity as an HDAC inhibitor.

In one embodiment, Q^2 has a backbone of at least 4 atoms.
In one embodiment, Q^2 has a backbone of at least 5 atoms.
In one embodiment, Q^2 has a backbone of at least 6 atoms.

In one embodiment, Q^2 has a backbone of:
from 4 to 8 atoms;
from 4 to 7 atoms;
from 4 to 6 atoms; or,
from 4 to 5 atoms.

In one embodiment, Q^2 has a backbone of:
from 5 to 8 atoms; or
from 5 to 7 atoms; or
from 5 to 6 atoms.

In one embodiment, Q^2 has a backbone of from 5 to 6 atoms.

In one embodiment, Q^2 has a backbone of 4 atoms.
In one embodiment, Q^2 has a backbone of 5 atoms.
In one embodiment, Q^2 has a backbone of 6 atoms.
In one embodiment, Q^2 has a backbone of 7 atoms.
In one embodiment, Q^2 has a backbone of 8 atoms.

In one embodiment, the backbone of "atoms" is a backbone of "carbon atoms."

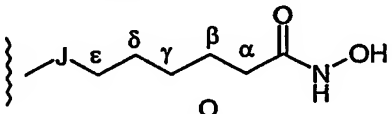
Note that, for embodiments which are characterised by, or further characterised by, a backbone length limitation, corresponding changes in the description of that embodiment may be implicit. For example, for an embodiment wherein (a) Q^2 is a partially unsaturated C_{2-8}alkylene group and (b) Q^2 has a backbone of 4 carbon atoms, the term "C_{2-8}alkylene" group is necessarily, and implicitly, interpreted as "C_{4-8}alkylene."

The Acid Leader Group, Q^2: Substitution

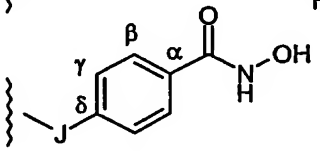
In one embodiment, Q^2 is unsubstituted.
In one embodiment, Q^2 is optionally substituted.
In one embodiment, Q^2 is substituted.

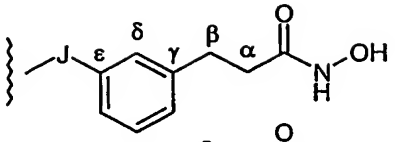
The backbone atoms of the acid leader group, Q^2, which link J and the carbamic acid group (-C(=O)NHOH), are denoted α, β, γ, δ, etc., starting with the backbone atom adjacent to the carbamic acid group. Some examples are illustrated below.

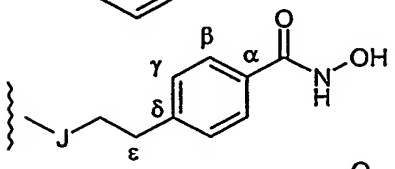
Q^2 is alkylene

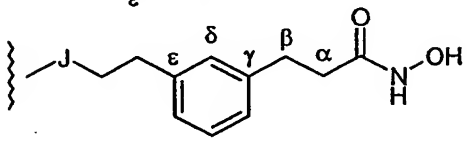


Q^2 is arylene



Q^2 is arylene-alkylene 

Q^2 is alkylene-arylene 

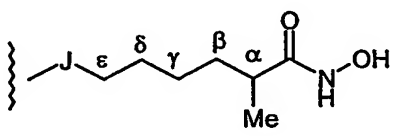
Q^2 is alkylene-arylene-alkylene 

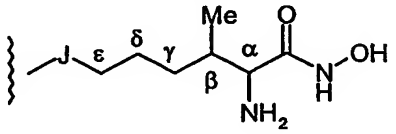
Without wishing to be bound to any particular theory, it is believed that groups (e.g., substituents), particularly bulky groups (e.g., substituents), at the α-position, or at either or both of the α- and β -positions, prevent or reduce the interaction of the carbamic acid group (-C(=O)NHOH) with HDAC (or its complexes), and thereby reduce the compound's activity as an HDAC inhibitor.

In one embodiment, Q^2 is, additionally, unsubstituted at the α-position.

In one embodiment, Q^2 is, additionally, unsubstituted at the α-position and unsubstituted at the β-position.

Note that, in some embodiments, Q^2 may have a non-linear alkylene group (for example, a branched alkylene) adjacent to the carbamic acid group. An example, wherein Q^2 is a branched saturated C_6-alkylene, having a methyl group at the α-position, is shown below. Although there is a group (i.e., a methyl group) at the α-position, such compounds are unsubstituted at the α-position, because the α-methyl group itself is considered to be part of the unsubstituted Q^2. Another example, wherein Q^2 is a branched saturated C_6-alkylene, having an amino group at the α-position and a methyl group at the β-position, is shown below; such compounds are α-substituted, β-unsubstituted.





In one embodiment, in which Q^2 is a group as defined herein (e.g., C_{4-8}alkylene, C_{5-20}arylene-C_{1-7}alkylene, C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene) having an alkylene group adjacent to the carbamic acid group, Q^2 is, additionally, unsubstituted at the α-position.

In one embodiment, in which Q^2 is a group as defined herein (e.g., C_{4-8}alkylene, C_{5-20}arylene-C_{1-7}alkylene, C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene) having an alkylene group adjacent to the carbamic acid group, that adjacent alkylene group has a $-CH_2-$ or =CH- group adjacent to the carbamic acid group (that is, at the α-position).

In one embodiment, in which Q^2 is a group as defined herein (e.g., C_{4-8}alkylene, C_{5-20}arylene-C_{1-7}alkylene, C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene) having an alkylene group adjacent to the carbamic acid group, that adjacent alkylene group has a $-CH_2-$ group adjacent to the carbamic acid group (that is, at the α-position).

In one embodiment, in which Q^2 is a group as defined herein (e.g., C_{4-8}alkylene, C_{5-20}arylene-C_{1-7}alkylene, C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene) having an alkylene group adjacent to the carbamic acid group, that adjacent alkylene group has a =CH- group adjacent to the carbamic acid group (that is, at the α-position).

In one embodiment, in which Q^2 is a group as defined herein (e.g., C_{4-8}alkylene, C_{5-20}arylene-C_{1-7}alkylene, C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene) having an alkylene group adjacent to the carbamic acid group, Q^2 is, additionally, unsubstituted at the α-position and unsubstituted at the β -position.

In one embodiment, in which Q^2 is a group as defined herein (e.g., C_{4-8}alkylene, C_{5-20}arylene-C_{1-7}alkylene, C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene) having an alkylene group adjacent to the carbamic acid group, that adjacent alkylene group has a $-CH_2CH_2-$, -CH=CH-, or -C≡C- group adjacent to the carbamic acid group (that is, at the α,β-position).

In one embodiment, in which Q^2 is a group as defined herein (e.g., C_{4-8}alkylene, C_{5-20}arylene-C_{1-7}alkylene, C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene) having an alkylene group adjacent to the carbamic acid group, that adjacent alkylene group has a $-CH_2CH_2-$ or -CH=CH- group adjacent to the carbamic acid group (that is, at the α,β-position).

In one embodiment, in which Q^2 is a group as defined herein (e.g., C_{4-8}alkylene, C_{5-20}arylene-C_{1-7}alkylene, C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene) having an alkylene group adjacent to the carbamic acid group, that adjacent alkylene group has a $-CH_2CH_2-$ group adjacent to the carbamic acid group (that is, at the α,β-position).

In one embodiment, in which Q^2 is a group as defined herein (e.g., C_{4-8}alkylene, C_{5-20}arylene-C_{1-7}alkylene, C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene) having an alkylene group adjacent to the carbamic acid group, that adjacent alkylene group has a -CH=CH- group adjacent to the carbamic acid group (that is, at the α,β-position).

Examples of substituents on Q^2 include, but are not limited to, those described under the heading "Substituents" below.

In one embodiment, the optional substituents on Q^2 are as defined under the heading "The Cyclyl Group, Cy: Optionally Substituted Phenyl: Substituents."

The Acid Leader Group, Q^2: Alkylene

In one embodiment, the acid leader group, Q^2, is C_{4-8}alkylene, and is optionally substituted, and has a backbone length of at least 4 atoms.

In one embodiment, Q^2 is independently a saturated C_{4-8}alkylene group.

In one embodiment, Q^2 is independently a partially unsaturated C_{4-8}alkylene group.

In one embodiment, Q^2 is independently an aliphatic C_{4-8}alkylene group

In one embodiment, Q^2 is independently a linear C_{4-8}alkylene group.

In one embodiment, Q^2 is independently a branched C_{4-8}alkylene group.

In one embodiment, Q^2 is independently an alicyclic C_{4-8}alkylene group.

In one embodiment, Q^2 is independently a saturated aliphatic C_{4-8}alkylene group.

In one embodiment, Q^2 is independently a saturated linear C_{4-8}alkylene group.

In one embodiment, Q^2 is independently a saturated branched C_{4-8}alkylene group.

In one embodiment, Q^2 is independently a saturated alicyclic C_{4-8}alkylene group.

In one embodiment, Q^2 is independently a partially unsaturated aliphatic C_{4-8}alkylene group.

In one embodiment, Q^2 is independently a partially unsaturated linear C_{4-8}alkylene group.

In one embodiment, Q^2 is independently a partially unsaturated branched C_{4-8}alkylene group.

In one embodiment, Q^2 is independently a partially unsaturated alicyclic C_{4-8}alkylene group.

Note that, for embodiments excluding, e.g., certain backbone lengths, absence of adjacent carbon-carbon double bonds, etc., it is to be understood that the corresponding species listed below are similarly excluded from the respective embodiments discussed below.

In one embodiment, Q^2 is independently selected from:

$-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_8-$;

$-CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH(CH_3)-$;

$-CH(CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2CH(CH_3)-$, $-CH(CH_3)CH_2CH_2CH_2CH(CH_3)-$;

$-CH(CH_2CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_2CH_3)CH_2CH_2-$, $-CH_2CH_2CH(CH_2CH_3)CH_2-$, $-CH_2CH_2CH_2CH(CH_2CH_3)-$;

$-CH(CH_2CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_2CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_2CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_2CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2CH(CH_2CH_3)-$;

$-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CH_2CH=CH-$;

$-CH=CHCH_2CH_2CH_2-$, $-CH_2CH=CHCH_2CH_2-$, $-CH_2CH_2CH=CHCH_2-$, $-CH_2CH_2CH_2CH=CH-$;

-CH=CHCH$_2$CH$_2$CH$_2$CH$_2$-, -CH$_2$CH=CHCH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH=CHCH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$CH=CHCH$_2$-, -CH$_2$CH$_2$CH$_2$CH$_2$CH=CH-;

-CH=CHCH=CH-;

-CH=CHCH=CHCH$_2$-, -CH$_2$CH=CHCH=CH-, -CH=CHCH$_2$CH=CH-;

-CH=CHCH=CHCH$_2$CH$_2$-, -CH=CHCH$_2$CH=CHCH$_2$-, -CH=CHCH$_2$CH$_2$CH=CH-, -CH$_2$CH=CHCH=CHCH$_2$-, -CH$_2$CH=CHCH$_2$CH=CH-, -CH$_2$CH$_2$CH=CHCH=CH-;

-C(CH$_3$)=CHCH=CH-, -CH=C(CH$_3$)CH=CH-, -CH=CHC(CH$_3$)=CH-, -CH=CHCH=C(CH$_3$)-;

-C≡CCH$_2$CH$_2$-, -CH$_2$C≡CCH$_2$-, -CH$_2$CH$_2$C≡C-;

-C≡CCH(CH$_3$)CH$_2$-, -C≡CCH$_2$CH(CH$_3$)-;

-CH(CH$_3$)C≡CCH$_2$-, -CH$_2$C≡CCH(CH$_3$)-;

-CH(CH$_3$)CH$_2$C≡C-, -CH$_2$CH(CH$_3$)C≡C-;

-C≡CCH=CH-, -CH=CHC≡C-, -C≡CC≡C-;

-C≡CCH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$C≡C-;

-C≡CCH$_2$CH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$CH$_2$C≡C-;

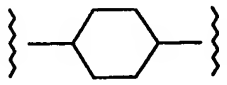
-C≡CCH=CHCH=CH-, -CH=CHC≡C-CH=CH-, -CH=CHCH=CHC≡C-;

-C(CH$_3$)=CHC≡C-, -CH=C(CH$_3$)C≡C-, -C≡CC(CH$_3$)=CH-, -C≡CCH=C(CH$_3$)-;

cyclopentylene cyclopentenylene;

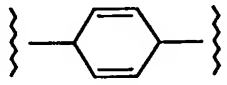
cyclohexylene, cyclohexenylene, cyclohexadienylene;

(cyclohex-1,4-ylene)

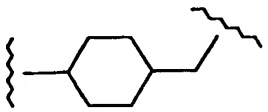


(2-cyclohexen-1,4-ylene)

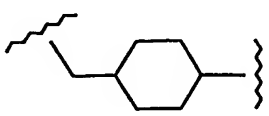
(2,5-cyclohexadien-1,4-ylene)



(cyclohex-1,4-ylene-methylene)



(methylene-cyclohex-1,4-ylene)



In one preferred embodiment, Q^2 is independently selected from:

$-(CH_2)_5-$;

$-(CH_2)_6-$;

$-(CH_2)_7-$;

$-(CH_2)_8-$;

$-CH(CH_3)CH_2CH_2CH_2CH_2-$;

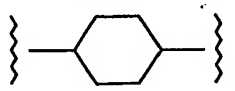
$-CH_2CH_2CH_2CH_2CH(CH_3)-$;

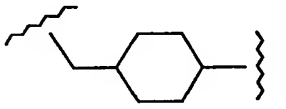
$-CH_2CH_2CH(CH_3)CH_2CH_2-$;

$-CH(CH_3)CH_2CH_2CH_2CH(CH_3)-$;

$-CH_2CH_2CH_2CH=CH-$;

$-CH_2CH_2CH_2CH_2CH=CH-$;

 and



In one preferred embodiment, Q^2 is independently selected from:

$-(CH_2)_5-$;

$-(CH_2)_6-$;

$-(CH_2)_7-$;

$-(CH_2)_8-$;

$-CH(CH_3)CH_2CH_2CH_2CH_2-$;

$-CH_2CH_2CH_2CH_2CH(CH_3)-$;

$-CH_2CH_2CH_2CH=CH-$; and,

$-CH_2CH_2CH_2CH_2CH=CH-$.

In one preferred embodiment, Q^2 is independently selected from:

$-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, and $-(CH_2)_8-$.

<u>The Acid Leader Group, Q^2: Arylene</u>

In one embodiment, the acid leader group, Q^2, is independently:

C_{5-20}arylene (denoted -Ar-),

and is optionally substituted,

and has a backbone length of at least 4 atoms.

In one embodiment, Q^2 is C_{5-20}arylene; and is optionally substituted.

In one embodiment, Q^2 is C_{5-6}arylene; and is optionally substituted.

In one embodiment, Q^2 is phenylene; and is optionally substituted.

In one embodiment, Q^2 additionally has a backbone length as described above under the heading "The Acid Leader Group, Q^2: Backbone Length."

The Acid Leader Group, Q^2:
Alkylene-Arylene, Arylene-Alkylene, and Alkylene-Arylene-Alkylene

In one preferred embodiment, the acid leader group, Q^2, is independently:

C_{5-20}arylene-C_{1-7}alkylene;

C_{1-7}alkylene-C_{5-20}arylene; or,

C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene;

and is optionally substituted;

and has a backbone length of at least 4 atoms.

In one preferred embodiment, the acid leader group, Q^2, is independently:

C_{5-20}arylene-C_{1-7}alkylene;

and is optionally substituted;

and has a backbone length of at least 4 atoms.

In one preferred embodiment, the acid leader group, Q^2, is independently:

C_{1-7}alkylene-C_{5-20}arylene; or,

and is optionally substituted;

and has a backbone length of at least 4 atoms.

In one preferred embodiment, the acid leader group, Q^2, is independently:

C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene;

and is optionally substituted;

and has a backbone length of at least 4 atoms.

In one preferred embodiment, Q^2 is independently:

C_{5-6}arylene-C_{1-7}alkylene;

C_{1-7}alkylene-C_{5-6}arylene; or,

C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene;

and is optionally substituted;

and has a backbone length of at least 4 atoms.

In one preferred embodiment, Q^2 is independently:

phenylene-C_{1-7}alkylene;

C_{1-7}alkylene-phenylene; or,

C_{1-7}alkylene-phenylene-C_{1-7}alkylene;

and is optionally substituted;

and has a backbone length of at least 4 atoms.

In one embodiment, Q^2 is C_{1-7}alkylene-C_{5-20}arylene; and is optionally substituted.

In one embodiment, Q^2 is C_{1-7}alkylene-C_{5-6}arylene; and is optionally substituted.

In one embodiment, Q^2 is independently C_{1-7}alkylene-phenylene; and is optionally substituted.

In one embodiment, Q^2 is C_{5-20}arylene-C_{1-7}alkylene; and is optionally substituted.

In one embodiment, Q^2 is C_{5-6}arylene-C_{1-7}alkylene; and is optionally substituted.

In one embodiment, Q^2 is independently phenylene-C_{1-7}alkylene; and is optionally substituted.

In one embodiment, Q^2 is C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene; and is optionally substituted.

In one embodiment, Q^2 is C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene; and is optionally substituted.

In one embodiment, Q^2 is independently C_{1-7}alkylene-phenylene-C_{1-7}alkylene; and is optionally substituted.

In the above arylene-alkylene (denoted -Ar-R^{Q22}-), alkylene-arylene (denoted -R^{Q21}-Ar-), and alkylene-arylene-alkylene (denoted -R^{Q21}-Ar-R^{Q22}) groups, each of R^{Q21} and R^{Q22} is independently C_{1-7}alkylene.

In one embodiment, in the above arylene-alkylene, alkylene-arylene, and alkylene-arylene-alkylene groups, each alkylene group is independently:

(a) a saturated C_{1-7}alkylene group; or:

(b) a partially unsaturated C_{2-7}alkylene group; or:

(c) an aliphatic C_{1-7}alkylene group; or:

(d) a linear C_{1-7}alkylene group; or:

(e) a branched C_{2-7}alkylene group; or:

(f) a saturated aliphatic C_{1-7}alkylene group; or:

(g) a saturated linear C_{1-7}alkylene group; or:

(h) a saturated branched C_{2-7}alkylene group; or:

(i) a partially unsaturated aliphatic C_{2-7}alkylene group; or:

(j) a partially unsaturated linear C_{2-7}alkylene group; or:

(k) a partially unsaturated branched C_{2-7}alkylene group;

and is optionally substituted.

In one embodiment, Q^2 additionally has a backbone length as described above under the heading "The Acid Leader Group, Q^2: Backbone Length."

Alkylene Groups R^{Q21} and R^{Q22}: Certain Embodiments

Note that, for embodiments excluding, e.g., certain backbone lengths, absence of adjacent carbon-carbon double bonds, etc., it is to be understood that the corresponding species listed below are similarly excluded from the respective embodiments discussed below.

In one embodiment, each of R^{Q21} and R^{Q22} is independently as defined for Q^1 under the heading "The Cyclyl Leader Group, Q^1: Alkylene: Certain Embodiments."

In one embodiment, R^{Q21} is independently selected from:

$-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$,

$-CH_2-CH=CH-$; and,

$-CH_2-CH=CH-CH=CH-$.

In one embodiment, R^{Q21} is independently selected from:

$-CH_2-$, $-CH_2CH_2-$, and $-CH_2-CH=CH-$.

In one embodiment, R^{Q21} is independently selected from:

$-CH_2-$ and , $-CH_2CH_2-$.

In one embodiment, R^{Q21} is independently $-CH_2-$.

In one embodiment, R^{Q21} is independently $-CH_2CH_2-$.

In one embodiment, R^{Q21} is independently $-CH_2-CH=CH-$.

In one embodiment, R^{Q21} is independently cis $-CH_2-CH=CH-$.

In one embodiment, R^{Q21} is independently trans $-CH_2-CH=CH-$.

In one embodiment, R^{Q22} is independently selected from:

$-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$;

$-CH=CH-$;

$-CH_2-CH=CH-$;

$-CH=CH-CH=CH-$; and,

$-CH_2-CH=CH-CH=CH-$.

In one embodiment, R^{Q22} is independently selected from:

$-CH_2-$, $-CH_2CH_2-$, $-CH=CH-$, and $-CH_2-CH=CH-$.

In one embodiment, R^{Q22} is independently selected from:

$-CH_2-$, $-CH_2CH_2-$, and $-CH=CH-$.

The Acid Leader Group, Q^2: Certain Phenylene-Containing Embodiments

In one embodiment, Q^2 is independently:

phenylene;

and is optionally substituted;

and has a backbone length of at least 4 atoms.

In one embodiment, Q^2 is independently:

methylene-phenylene;

ethylene-phenylene;

and is optionally substituted;

and has a backbone length of at least 4 atoms.

In one embodiment, Q^2 is independently:

phenylene-methylene;

phenylene-ethylene; or,

phenylene-ethenylene (also known as phenylene-vinylene);

and is optionally substituted;

and has a backbone length of at least 4 atoms.

In one embodiment, Q^2 is independently:

methylene-phenylene-methylene;

methylene-phenylene-ethylene;

methylene-phenylene-ethenylene;

ethylene-phenylene-methylene;

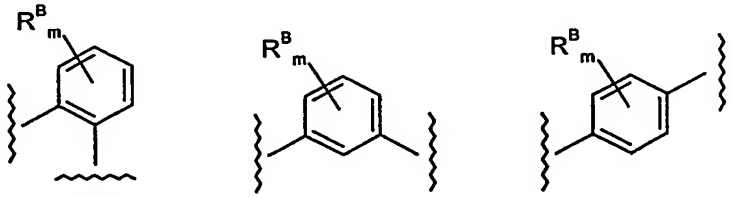
ethylene-phenylene-ethylene;

ethylene-phenylene-ethenylene;

and is optionally substituted;

and has a backbone length of at least 4 atoms.

In the above phenylene, phenylene-alkylene, alkylene-phenylene, and alkylene-phenylene-alkylene groups, the phenylene linkage may be ortho (i.e., 1,2-), meta (i.e., 1,3-), or para (i.e., 1,4-), and the phenylene group is optionally substituted with from 1 to 4 substituents, R^B:



ortho meta para

In one embodiment, the phenylene linkage is meta or para.

In one embodiment, the phenylene linkage is meta.

In one embodiment, the phenylene linkage is para.

In one embodiment, m is an integer from 0 to 4.

In one embodiment, m is an integer from 0 to 3.

In one embodiment, m is an integer from 0 to 2.

In one embodiment, m is 0 or 1.

In one embodiment, m is an integer from 1 to 4.

In one embodiment, m is an integer from 1 to 3.

In one embodiment, m is 1 or 2.

In one embodiment, m is 4.

In one embodiment, m is 3.

In one embodiment, m is 2.

In one embodiment, m is 1.

In one embodiment, m is 0.

In one embodiment, the phenylene group is unsubstituted.

In one embodiment, the phenylene group is optionally substituted.

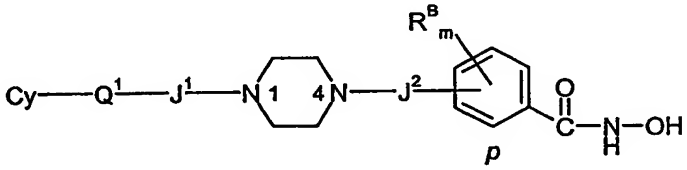
In one embodiment, the phenylene group is substituted.

Examples of substituents, R^B, include, but are not limited to, those described under the heading "Substituents" below.

In one embodiment, the substituents , R^B, are as defined under the heading "The Cyclyl Group, Cy: Optionally Substituted Phenyl: Substituents."

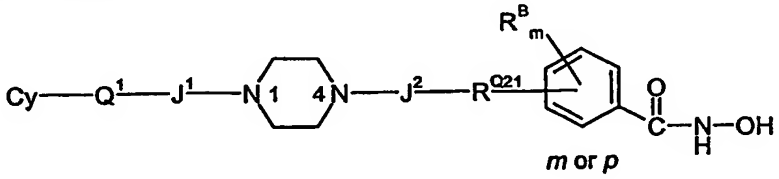
Examples of preferred substituents, R^B, include, but are not limited to, the following: fluoro, chloro, methyl, ethyl, isopropyl, t-butyl, trifluoromethyl, hydroxy, methoxy, ethoxy, isopropoxy, methylthio, amino, dimethylamino, diethylamino, morpholino, acetamido, nitro, and phenyl.

In one embodiment, the compounds have the following formula, in which Q^2 is para-arylene:



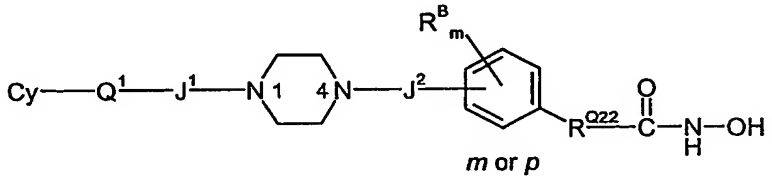
(9)

In one embodiment, the compounds have the following formula, in which Q^2 is alkylene-meta/para-arylene:



(10)

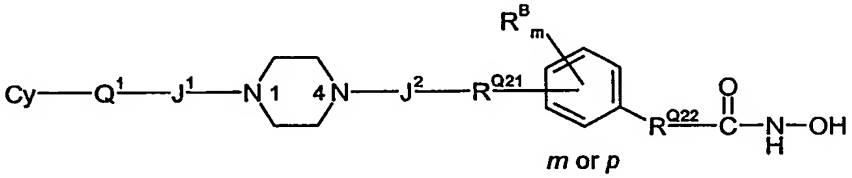
In one embodiment, the compounds have the following formula, in which Q^2 is arylene-meta/para-alkylene:



(11)

m or *p*

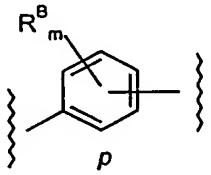
In one embodiment, the compounds have the following formula, in which Q^2 is alkylene-arylene-meta/para-alkylene:



(12)

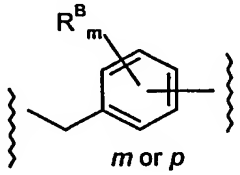
m or *p*

In one embodiment, Q^2 has the following formula (referred to herein as "para-phenylene"):



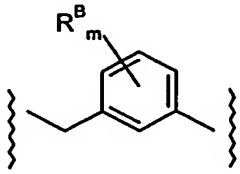
p

In one embodiment, Q^2 has the following formula (referred to herein as "methylene-meta/para-phenylene"):

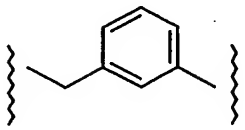


m or *p*

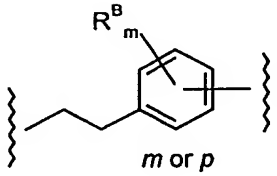
In one embodiment, Q^2 has the following formula (referred to herein as "methylene-meta-phenylene"):



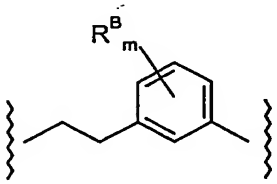
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted methylene-meta-phenylene"):



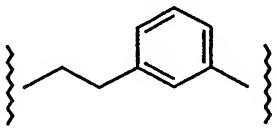
In one embodiment, Q^2 has the following formula (referred to herein as "ethylene-meta/para-phenylene"):



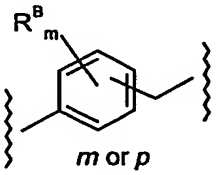
In one embodiment, Q^2 has the following formula (referred to herein as "ethylene-meta-phenylene"):



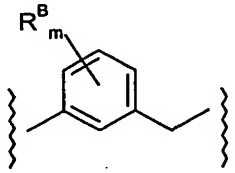
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted ethylene-meta-phenylene"):



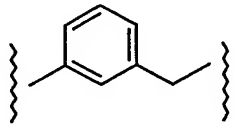
In one embodiment, Q^2 has the following formula (referred to herein as "phenylene-meta/para-methylene"):



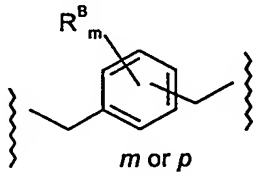
In one embodiment, Q^2 has the following formula (referred to herein as "phenylene-meta-methylene"):



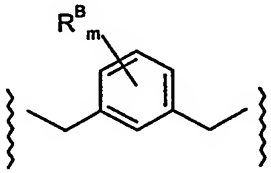
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted phenylene-meta-methylene"):



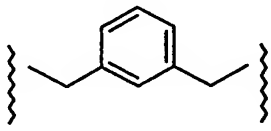
In one embodiment, Q^2 has the following formula (referred to herein as "methylene-phenylene-meta/para-methylene"):



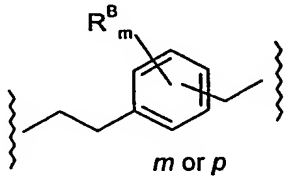
In one embodiment, Q^2 has the following formula (referred to herein as "methylene-phenylene-meta-methylene"):



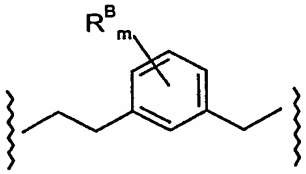
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted methylene-phenylene-meta-methylene"):



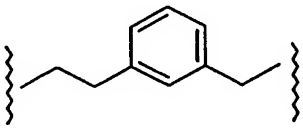
In one embodiment, Q^2 has the following formula (referred to herein as "ethylene-phenylene-meta/para-methylene"):



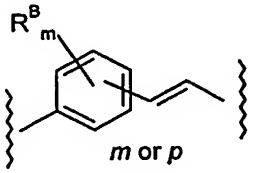
In one embodiment, Q^2 has the following formula (referred to herein as "ethylene-phenylene-meta-methylene"):



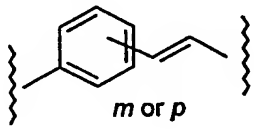
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted ethylene-phenylene-meta-methylene"):



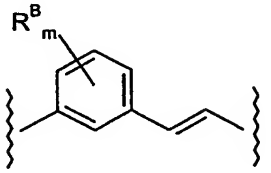
In one embodiment, Q^2 has the following formula (referred to herein as "phenylene-meta/para-trans-ethenylene"):



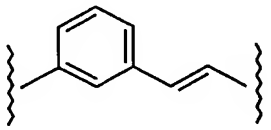
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted phenylene-meta/para-trans-ethenylene"):



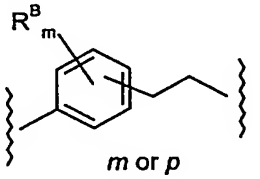
In one embodiment, Q^2 has the following formula (referred to herein as "phenylene-meta-trans-ethenylene"):



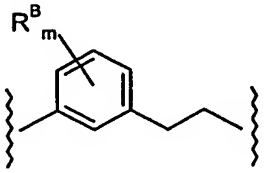
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted phenylene-meta-trans-ethenylene"):



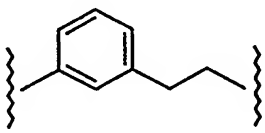
In one embodiment, Q^2 has the following formula (referred to herein as "phenylene-meta/para-ethylene"):



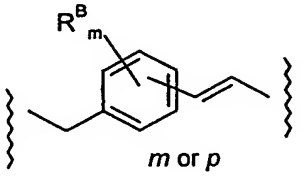
In one embodiment, Q^2 has the following formula (referred to herein as "phenylene-meta-ethylene"):



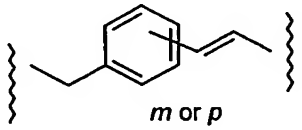
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted phenylene-meta-ethylene"):



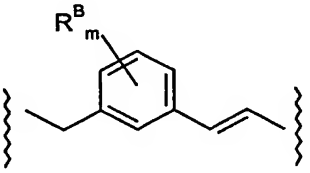
In one embodiment, Q^2 has the following formula (referred to herein as "methylene-phenylene-meta/para-trans-ethenylene"):



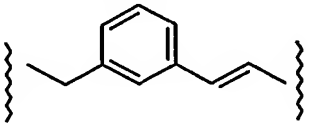
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted methylene-phenylene-meta/para-trans-ethenylene"):



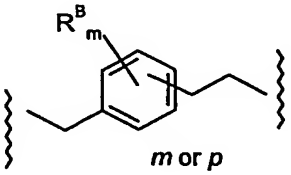
In one embodiment, Q^2 has the following formula (referred to herein as "methylene-phenylene-meta-trans-ethenylene"):



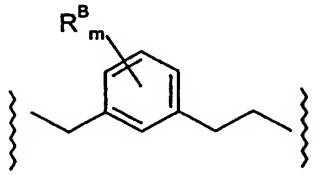
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted methylene-phenylene-meta-trans-ethenylene"):



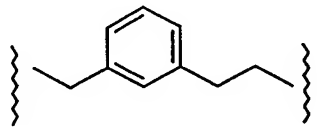
In one embodiment, Q^2 has the following formula (referred to herein as "methylene-phenylene-meta/para-ethylene"):



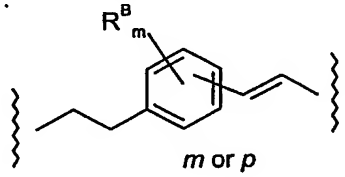
In one embodiment, Q^2 has the following formula (referred to herein as "methylene-phenylene-meta-ethylene"):



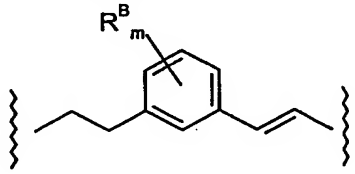
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted methylene-phenylene-meta-ethylene"):



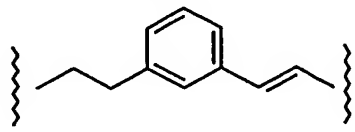
In one embodiment, Q^2 has the following formula (referred to herein as "ethylene-phenylene-meta/para-trans-ethenylene"):



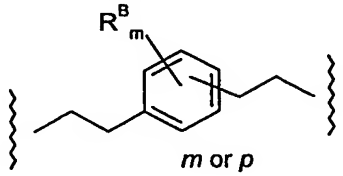
In one embodiment, Q^2 has the following formula (referred to herein as "ethylene-phenylene-meta-trans-ethenylene"):



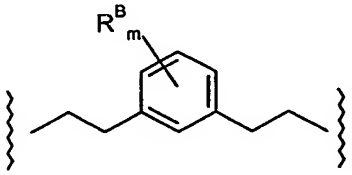
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted ethylene-phenylene-meta-trans-ethenylene"):



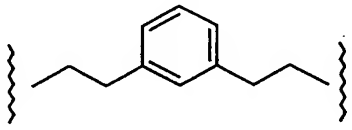
In one embodiment, Q^2 has the following formula (referred to herein as "ethylene-phenylene-meta/para-ethylene"):



In one embodiment, Q^2 has the following formula (referred to herein as "ethylene-phenylene-meta-ethylene"):



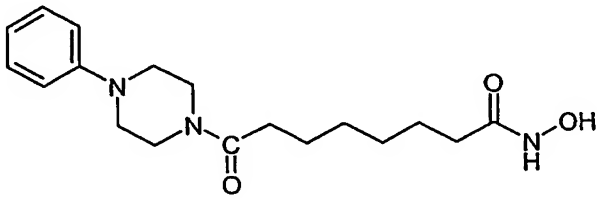
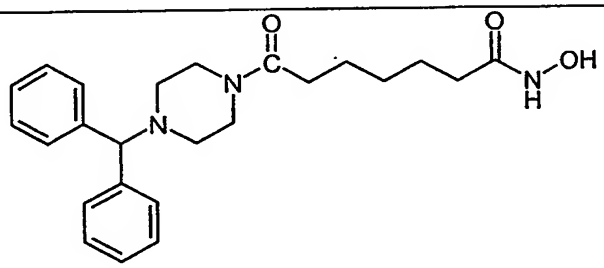
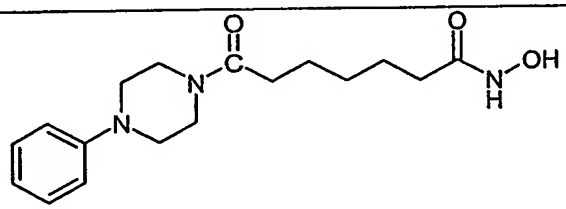
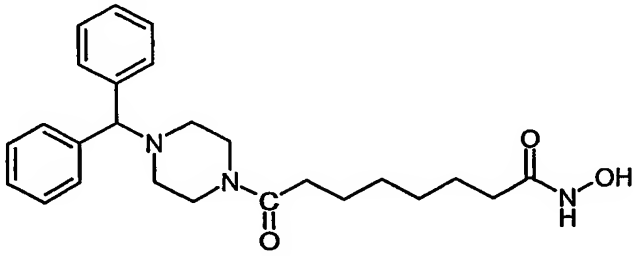
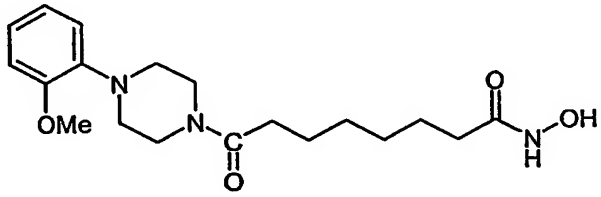
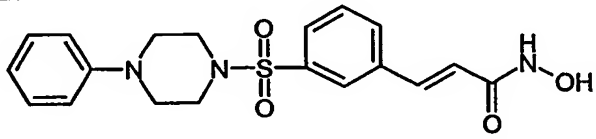
In one embodiment, Q^2 has the following formula (referred to herein as "unsubstituted ethylene-phenylene-meta-ethylene"):

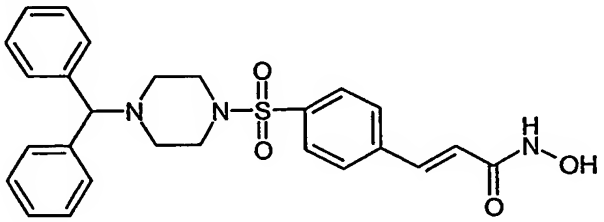
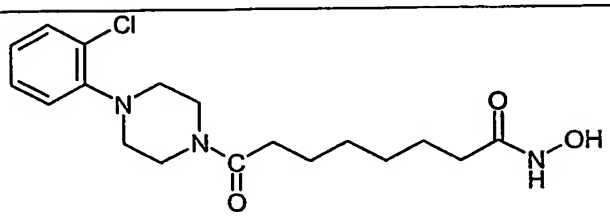
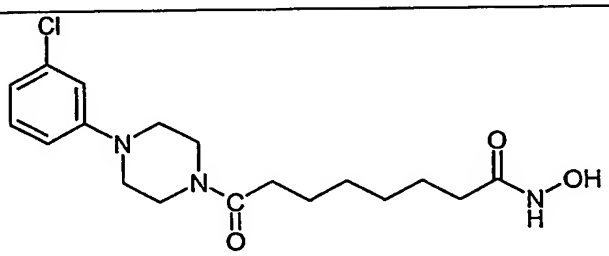
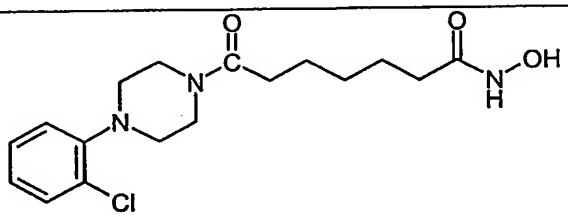
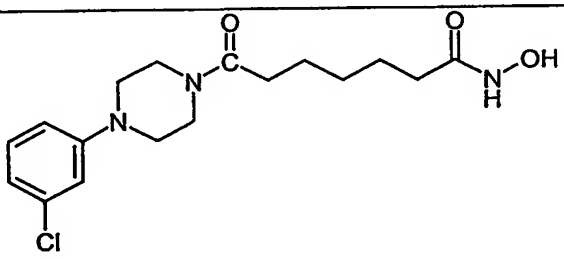
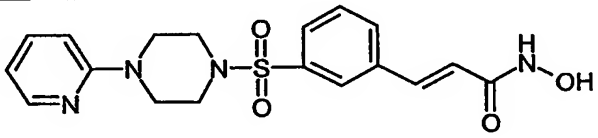
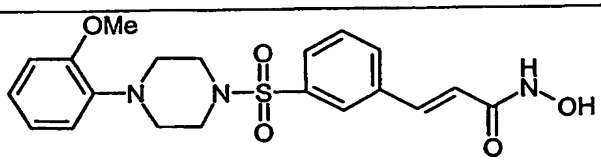


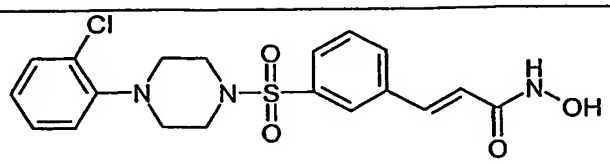
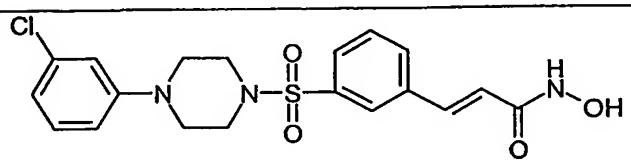
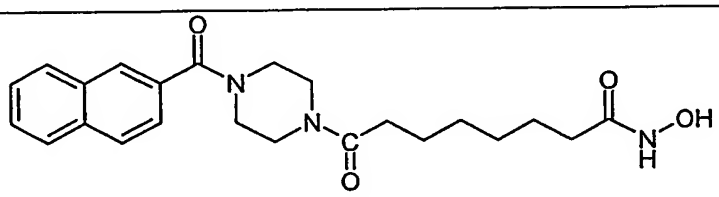
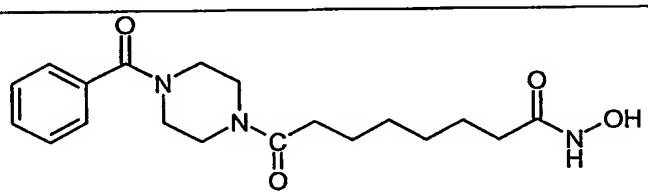
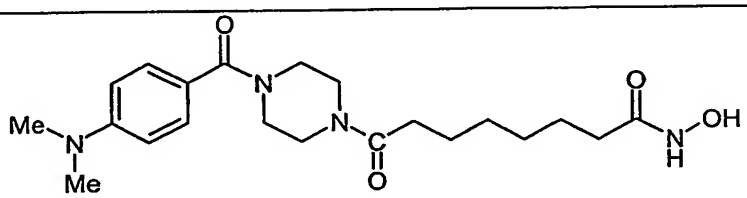
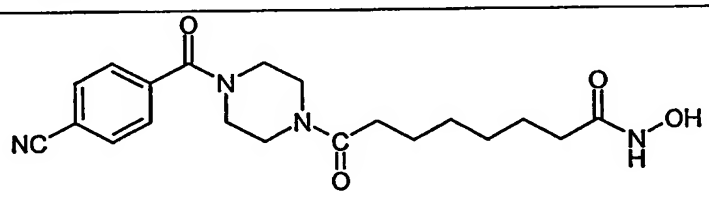
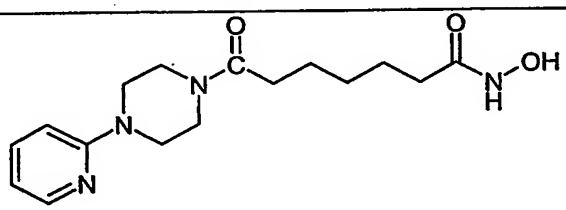
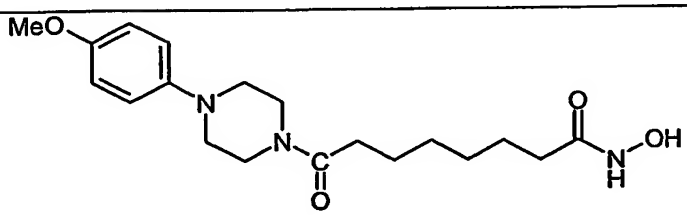
In one embodiment, Q^2 additionally has a backbone length as described above under the heading "The Acid Leader Group, Q^2: Backbone Length."

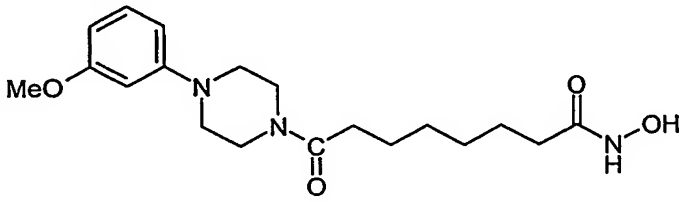
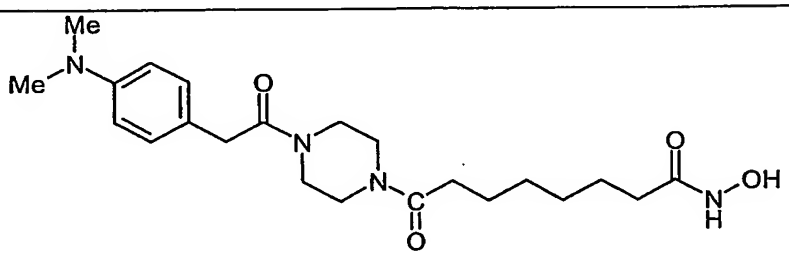
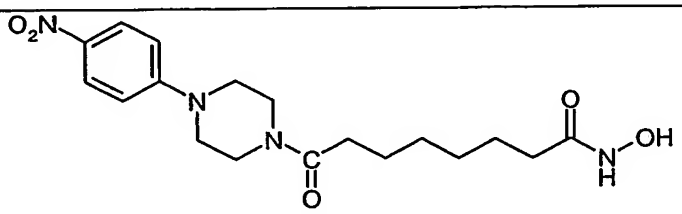
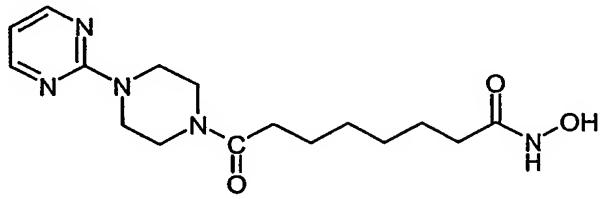
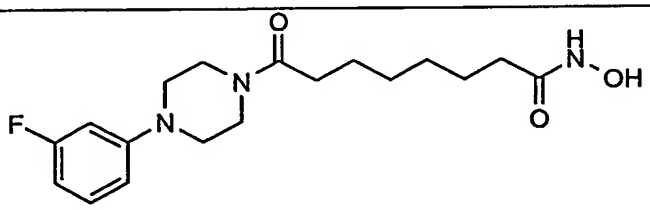
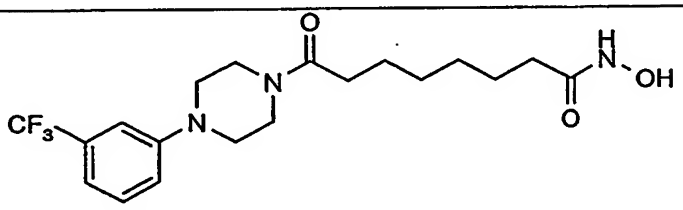
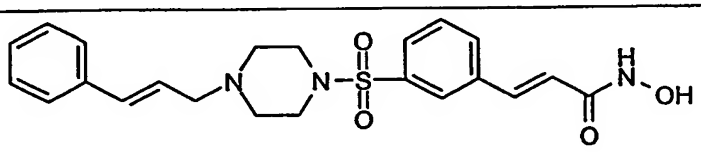
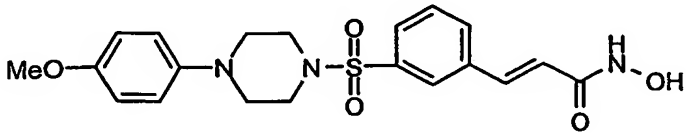
Examples of Specific Embodiments

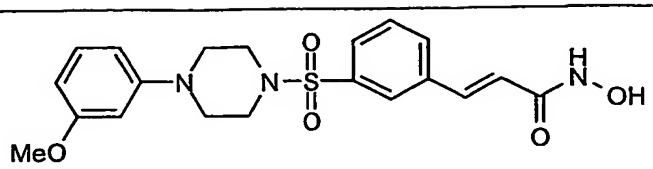
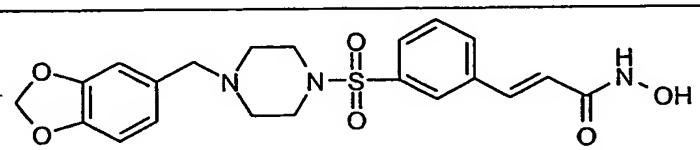
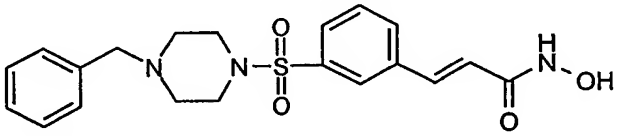
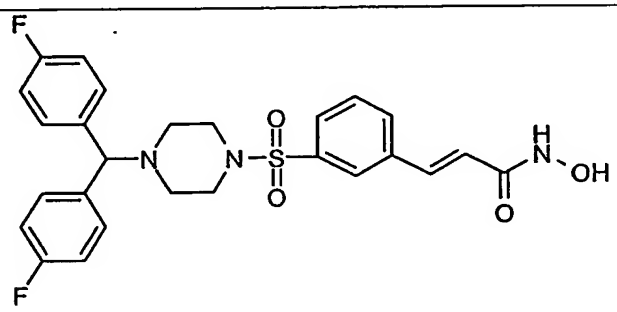
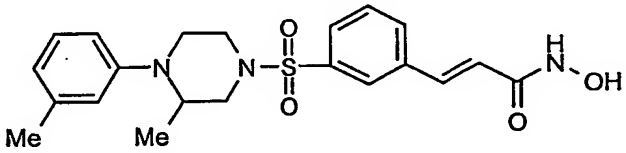
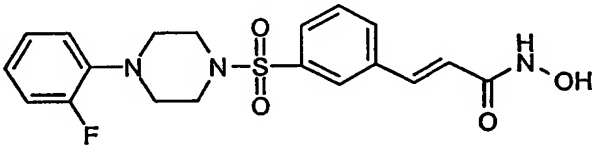
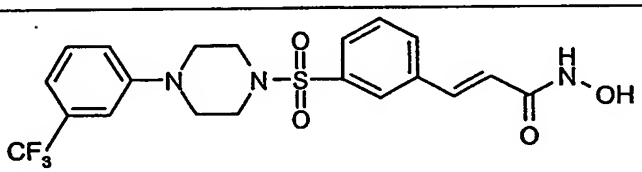
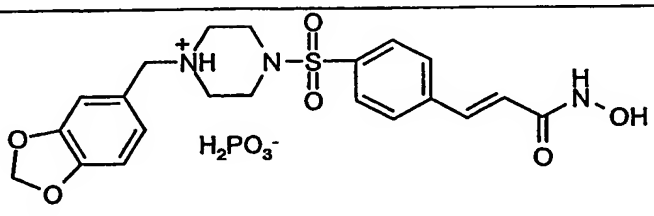
Some individual embodiments of the present invention include the following compounds.

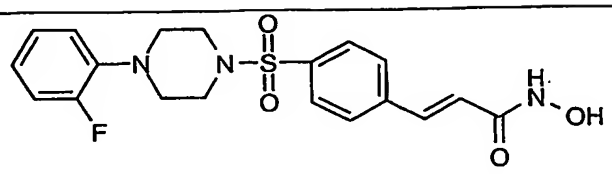
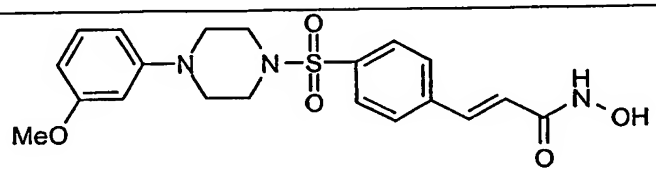
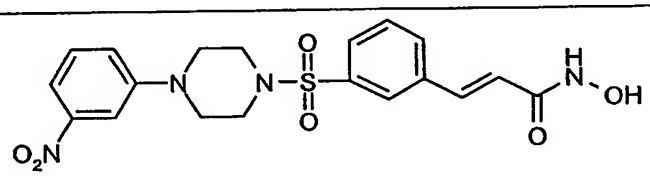
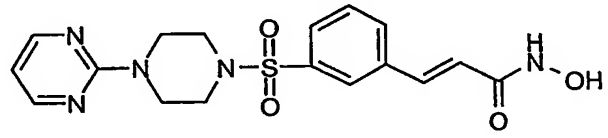
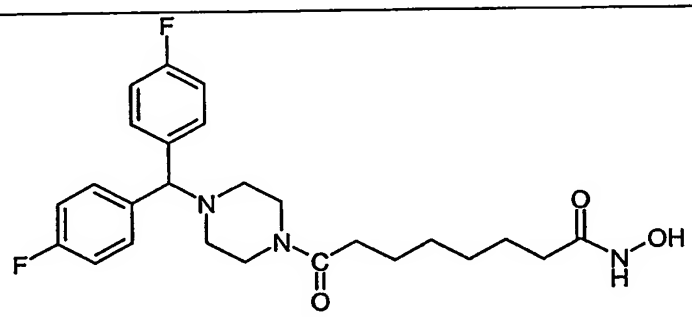
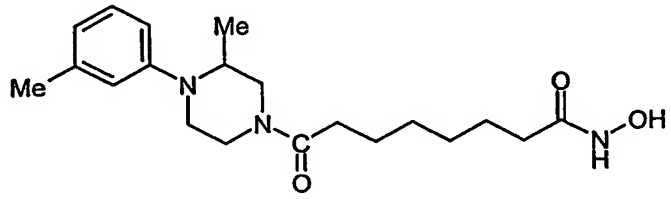
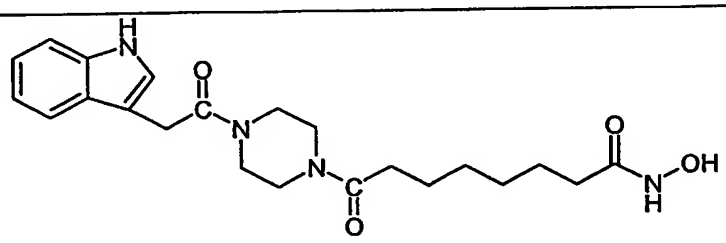
1.		PX117402 (Ex 140)
2.		PX117403 (Ex 141)
3.		PX117404 (Ex 142)
4.		PX117764 (Ex 143)
5.		PX117768 (Ex 144)
6.		PX118490 (Ex 40)

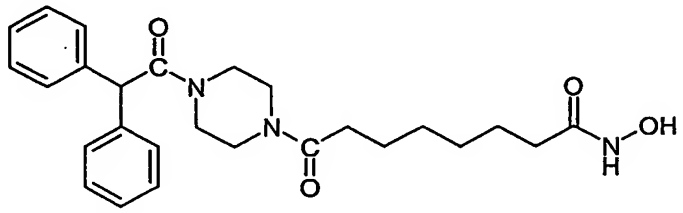
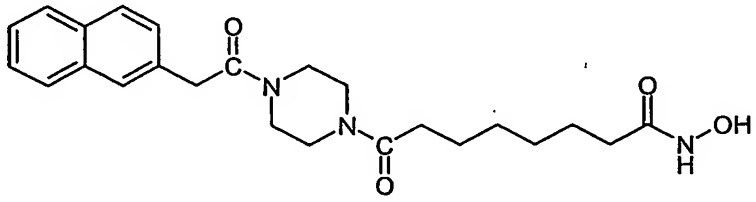
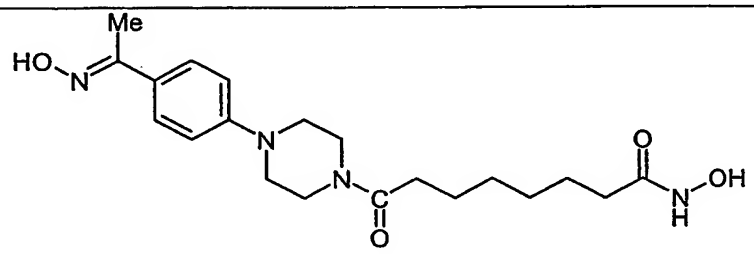
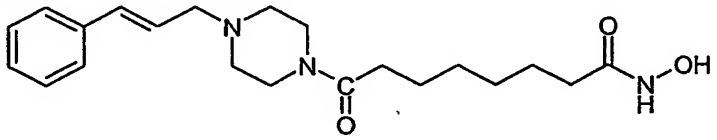
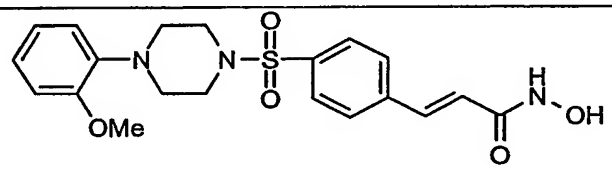
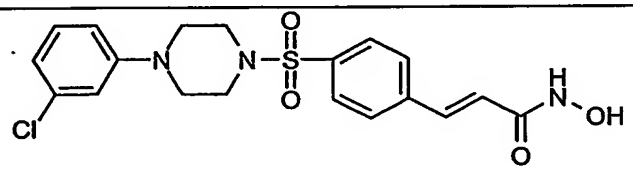
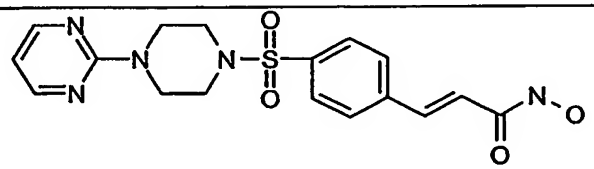
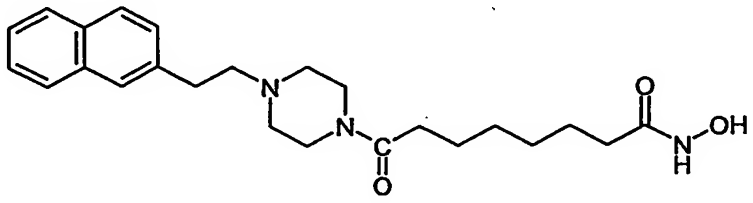
7.		PX118491 (Ex 41)
8.		PX118791 (Ex 145)
9.		PX118792 (Ex 146)
10.		PX118793 (Ex 147)
11.		PX118794 (Ex 148)
12.		PX118807 (Ex 45)
13.		PX118810 (Ex 42)

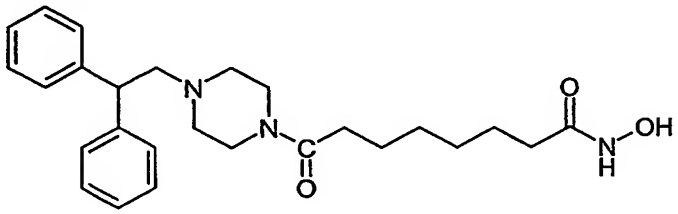
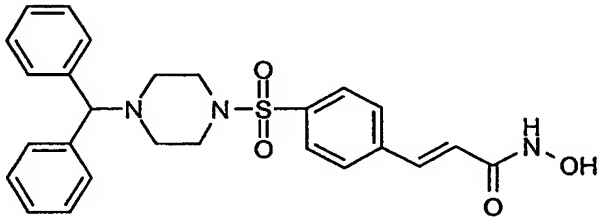
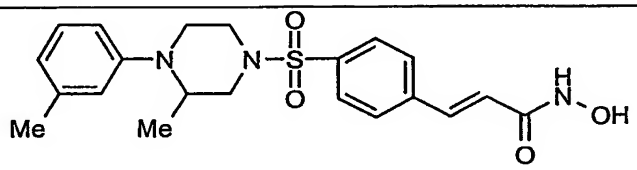
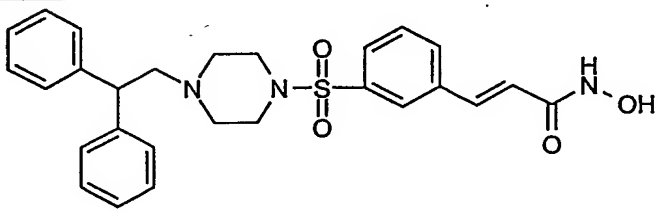
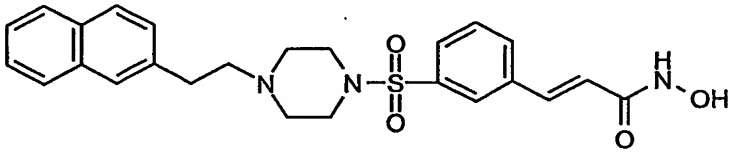
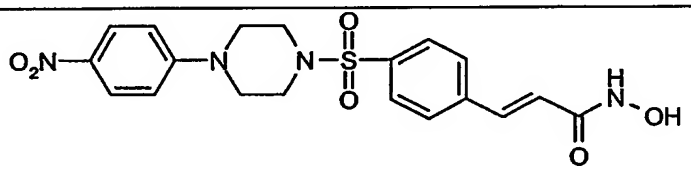
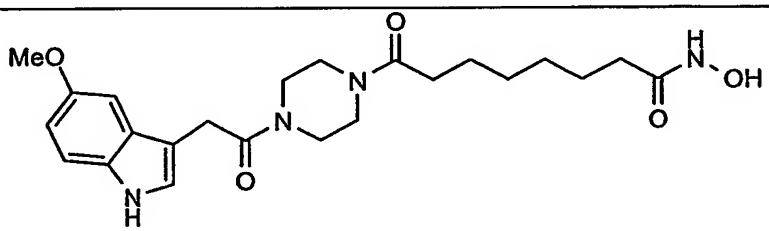
14.		PX118811 (Ex 43)
15.		PX118812 (Ex 44)
16.		PX118830 (Ex 149)
17.		PX118831 (Ex 150)
18.		PX118832 (Ex 151)
19.		PX118844 (Ex 163)
20.		PX118845 (Ex 164)
21.		PX118846 (Ex 152)

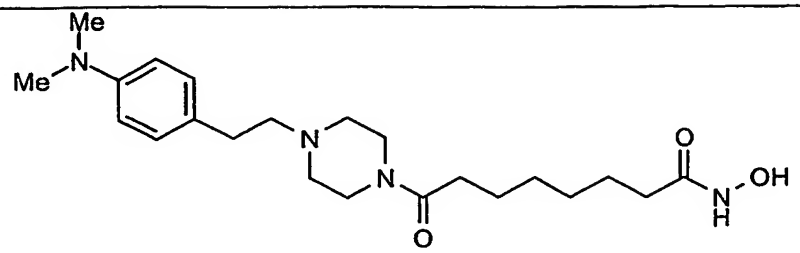
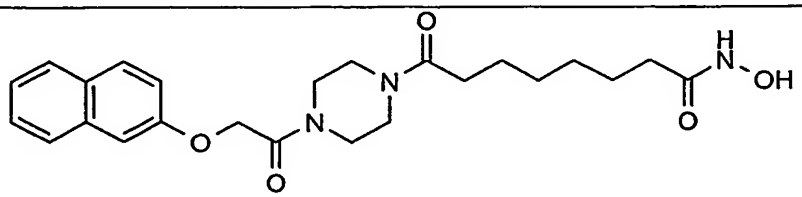
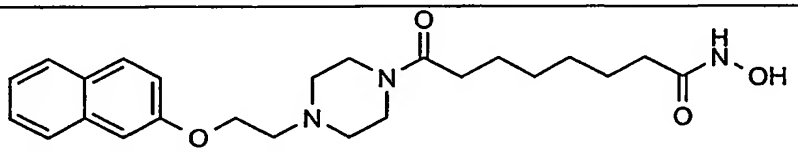
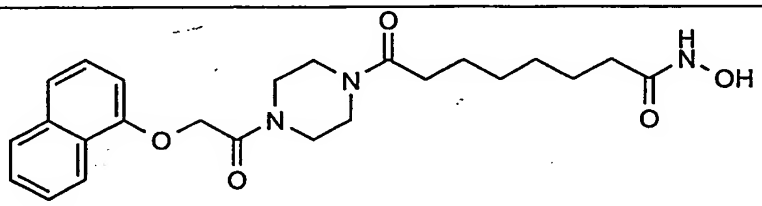
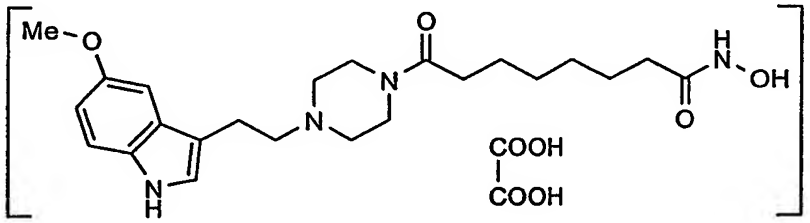
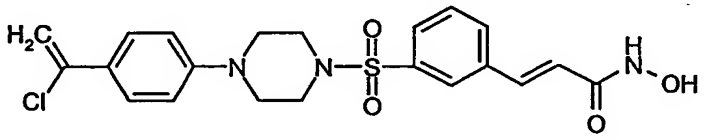
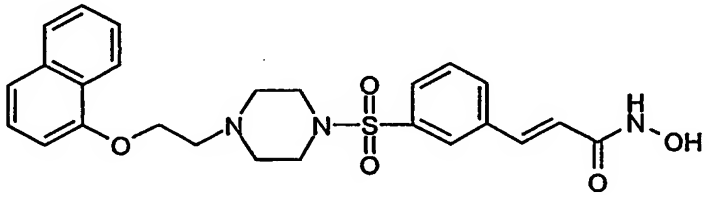
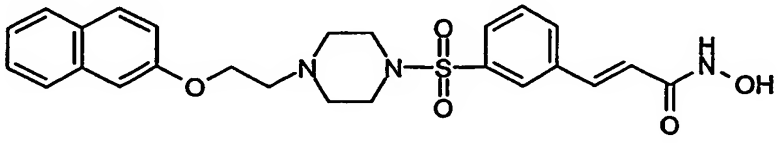
22.		PX118847 (Ex 153)
23.		PX118848 (Ex 165)
24.		PX118849 (Ex 154)
25.		PX118850 (Ex 166)
26.		PX118859 (Ex 174)
27.		PX118860 (Ex 175)
28.		PX118870 (Ex 52)
29.		PX118871 (Ex 53)

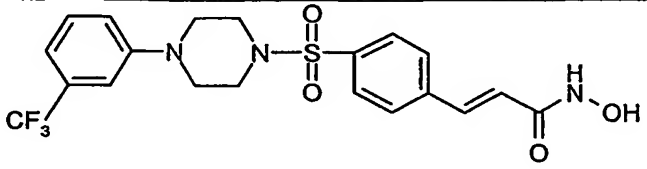
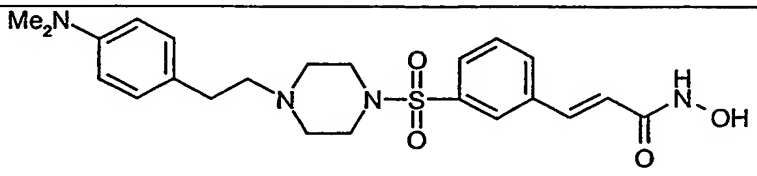
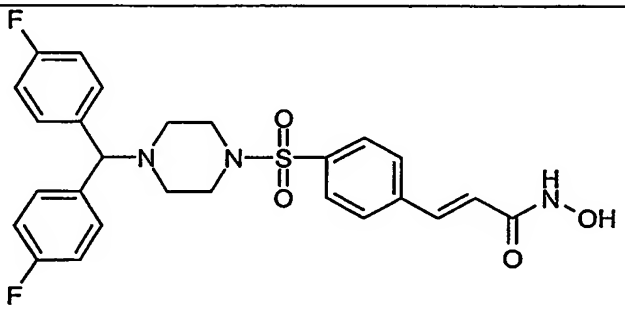
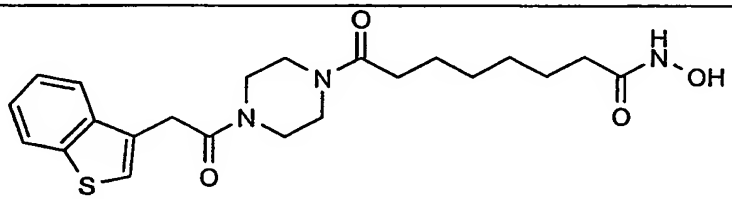
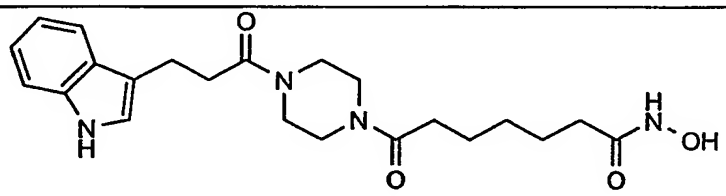
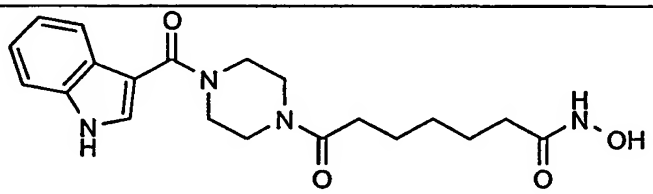
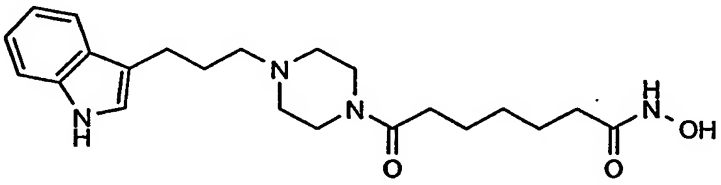
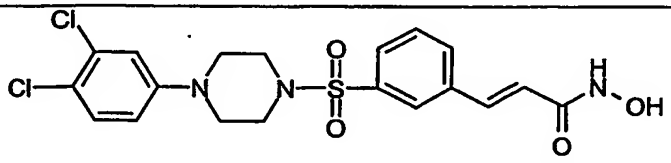
30.		PX118872 (Ex 54)
31.		PX118873 (Ex 55)
32.		PX118874 (Ex 56)
33.		PX118875 (Ex 57)
34.		PX118876 (Ex 58)
35.		PX118877 (Ex 59)
36.		PX118878 (Ex 60)
37.		PX118882 (Ex 72)

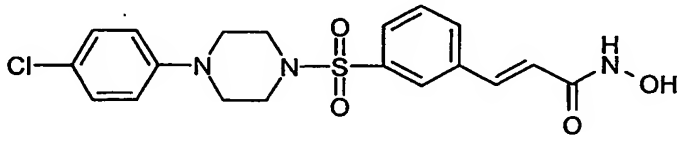
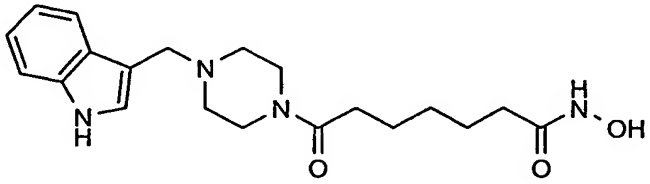
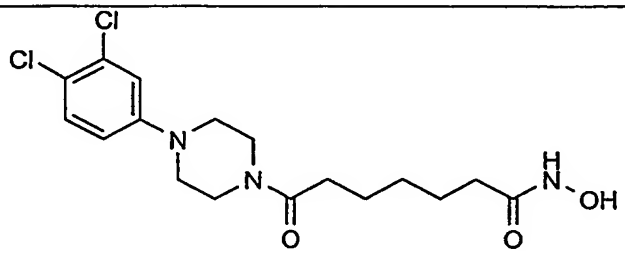
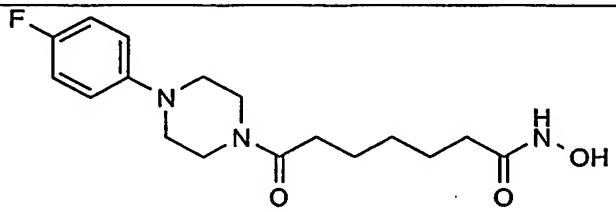
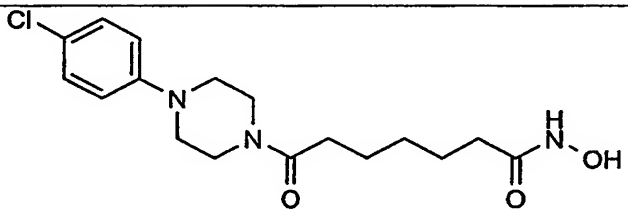
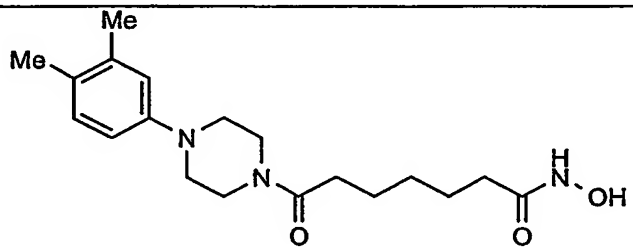
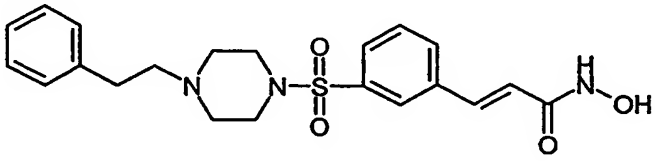
38.		PX118891 (Ex 74)
39.		PX118892 (Ex 75)
40.		PX118893 (Ex 61)
41.		PX118894 (Ex 62)
42.		PX118898 (Ex 176)
43.		PX118899 (Ex 177)
44.		PX118900 (Ex 178)

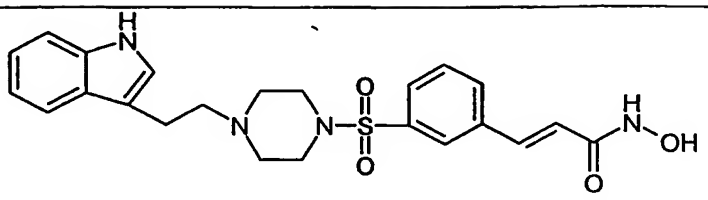
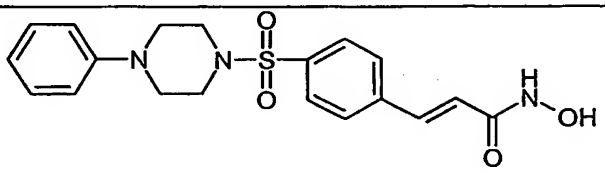
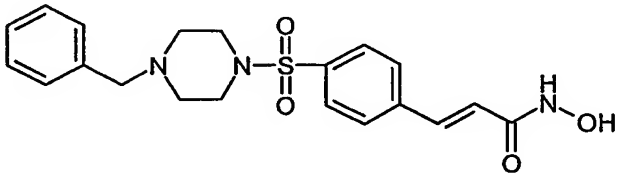
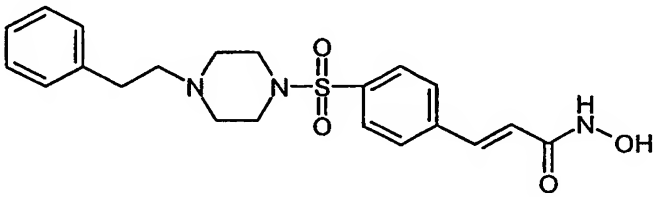
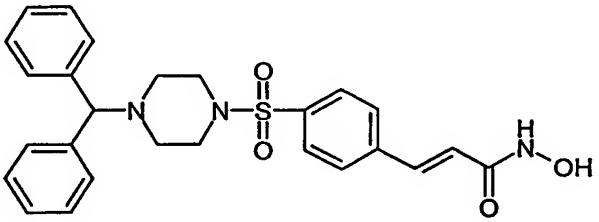
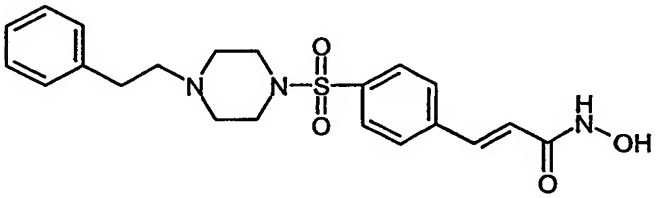
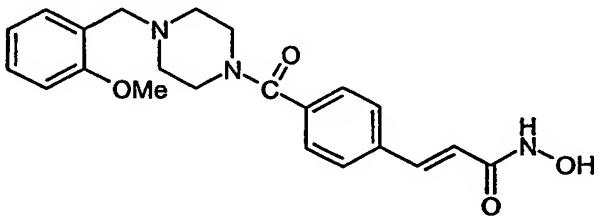
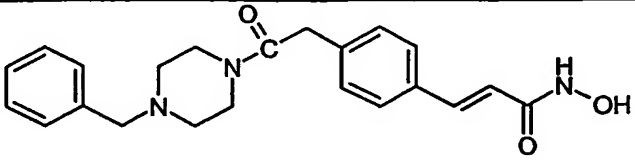
45.		PX118901 (Ex 179)
46.		PX118902 (Ex 180)
47.		PX118903 (Ex 181)
48.		PX118904 (Ex 182)
49.		PX118905 (Ex 76)
50.		PX118906 (Ex 77)
51.		PX118907 (Ex 78)
52.		PX118908 (Ex 183)

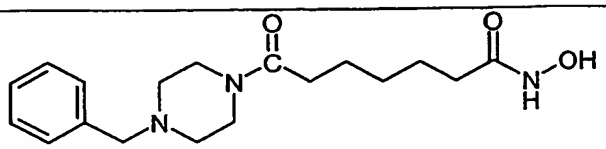
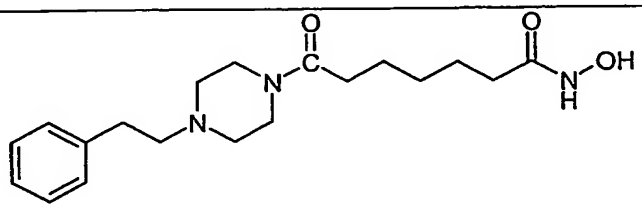
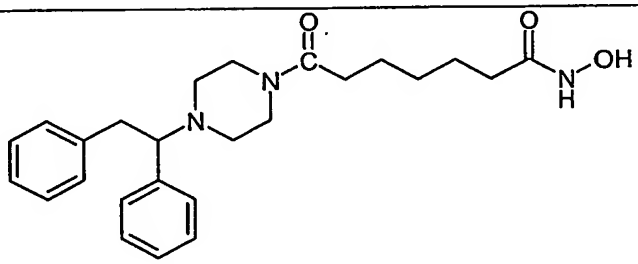
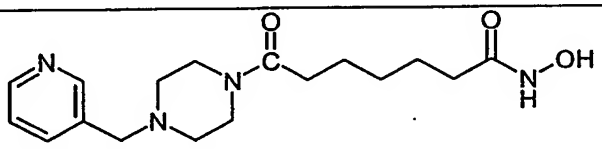
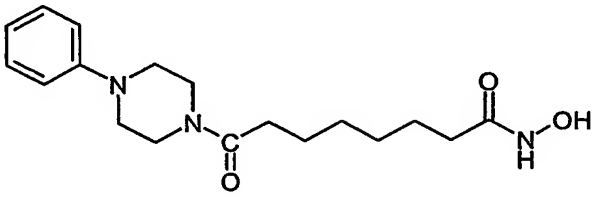
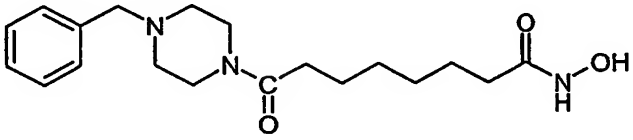
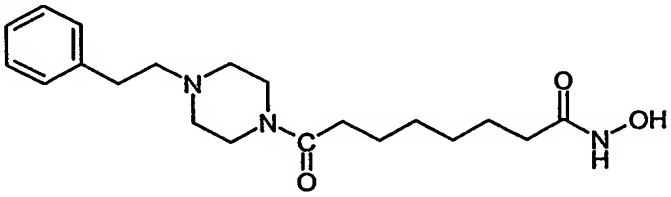
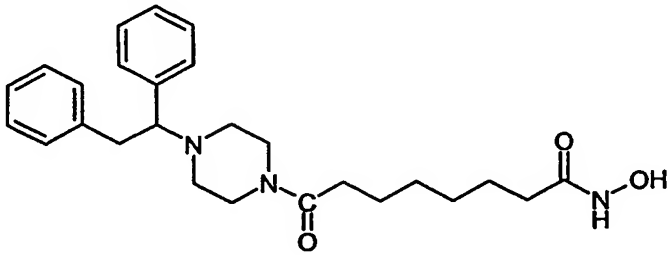
53.		PX118909 (Ex 184)
54.		PX118910 (Ex 79)
55.		PX118911 (Ex 80)
56.		PX118913 (Ex 63)
57.		PX118914 (Ex 64)
58.		PX118918 (Ex 73)
59.		PX118927 (Ex 155)

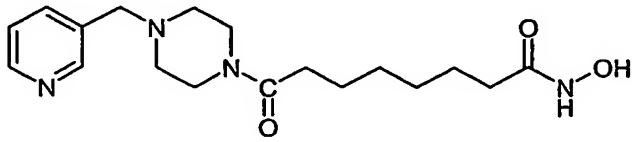
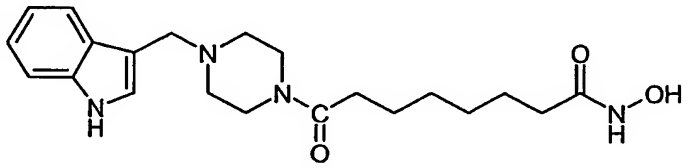
60.		PX118928 (Ex 167)
61.		PX118929 (Ex 168)
62.		PX118930 (Ex 156)
63.		PX118931 (Ex 157)
64.		PX118932 (Ex 158)
65.		PX118933 (Ex 46)
66.		PX118934 (Ex 48)
67.		PX118935 (Ex 49)

68.		PX118937 (Ex 70)
69.		PX118951 (Ex 47)
70.		PX118965 (Ex 71)
71.		PX118967 (Ex 159)
72.		PX118968 (Ex 169)
73.		PX118969 (Ex 170)
74.		PX118970 (Ex 171)
75.		PX118971 (Ex 50)

76.		PX118972 (Ex 51)
77.		PX118978 (Ex 172)
78.		PX118989 (Ex 160)
79.		PX118990 (Ex 161)
80.		PX118991 (Ex 162)
81.		PX118994 (Ex 173)
82.		

83.		
84.		
85.		
86.		
87.		
88.		
89.		
90.		

91.		
92.		
93.		
94.		
95.		
96.		
97.		
98.		

99.		
100.		

Note that, where the above examples are salts (e.g., PX118932, PX118882), other analogous salts may also be prepared.

Chemical Terms

The term "carbo," "carbyl," "hydrocarbo," and "hydrocarbyl," as used herein, pertain to compounds and/or groups which have only carbon and hydrogen atoms (but see "carbocyclic" below).

The term "hetero," as used herein, pertains to compounds and/or groups which have at least one heteroatom, for example, multivalent heteroatoms (which are also suitable as ring heteroatoms) such as boron, silicon, nitrogen, phosphorus, oxygen, sulfur, and selenium (more commonly nitrogen, oxygen, and sulfur) and monovalent heteroatoms, such as fluorine, chlorine, bromine, and iodine.

The term "saturated," as used herein, pertains to compounds and/or groups which do not have any carbon-carbon double bonds or carbon-carbon triple bonds.

The term "unsaturated," as used herein, pertains to compounds and/or groups which have at least one carbon-carbon double bond or carbon-carbon triple bond.

The term "aliphatic," as used herein, pertains to compounds and/or groups which are linear or branched, but not cyclic (also known as "acyclic" or "open-chain" groups).

The term "ring," as used herein, pertains to a closed ring of from 3 to 10 covalently linked atoms, more preferably 3 to 8 covalently linked atoms, yet more preferably 5 to 6 covalently linked atoms. A ring may be an alicyclic ring or an aromatic ring. The term "alicyclic ring," as used herein, pertains to a ring which is not an aromatic ring.

The term "carbocyclic ring," as used herein, pertains to a ring wherein all of the ring atoms are carbon atoms.

The term "carboaromatic ring," as used herein, pertains to an aromatic ring wherein all of the ring atoms are carbon atoms.

The term "heterocyclic ring," as used herein, pertains to a ring wherein at least one of the ring atoms is a multivalent ring heteroatom, for example, nitrogen, phosphorus, silicon, oxygen, or sulfur, though more commonly nitrogen, oxygen, or sulfur. Preferably, the heterocyclic ring has from 1 to 4 heteroatoms.

The term "cyclic compound," as used herein, pertains to a compound which has at least one ring. The term "cyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a cyclic compound.

Where a cyclic compound has two or more rings, they may be fused (e.g., as in naphthalene), bridged (e.g., as in norbornane), spiro (e.g., as in spiro[3.3]heptane), or a combination thereof. Cyclic compounds with one ring may be referred to as "monocyclic" or "mononuclear," whereas cyclic compounds with two or more rings may be referred to as "polycyclic" or "polynuclear."

The term "carbocyclic compound," as used herein, pertains to a cyclic compound which has only carbocyclic ring(s).

The term "heterocyclic compound," as used herein, pertains to a cyclic compound which has at least one heterocyclic ring.

The term "aromatic compound," as used herein, pertains to a cyclic compound which has at least one aromatic ring.

The term "carboaromatic compound," as used herein, pertains to a cyclic compound which has only carboaromatic ring(s).

The term "heteroaromatic compound," as used herein, pertains to a cyclic compound which has at least one heteroaromatic ring.

The term "monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment.

The term "monovalent monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment, via a single bond. Examples of such substituents include halo, hydroxy, and alkyl.

The term "multivalent monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment, but through a double bond or triple bond. Examples of such substituents include oxo, imino, alkylidene, and alklidyne.

The term "bidentate substituents," as used herein, pertains to substituents which have two points of covalent attachment, and which act as a linking group between two other moieties. Examples of such substituents include alkylene and arylene.

Substituents

The phrase "optionally substituted," as used herein, pertains to a parent group which may be unsubstituted or which may be substituted.

Unless otherwise specified, the term "substituted," as used herein, pertains to a parent group which bears one or more substituents. The term "substituent" is used herein in the conventional sense and refers to a chemical moiety which is covalently attached to, appended to, or if appropriate, fused to, a parent group. A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known.

The substituents are described in more detail below.

Alkyl: The term "alkyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl, cycloalkyl, etc., discussed below.

In this context, the prefixes (e.g., C_{1-4}, C_{1-7}, C_{1-20}, C_{2-7}, C_{3-7}, etc.) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C_{1-4}alkyl," as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups include C_{1-4}alkyl ("lower alkyl"), C_{1-7}alkyl, and C_{1-20}alkyl.

Examples of (unsubstituted) saturated alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), propyl (C_3), butyl (C_4), pentyl (C_5), hexyl (C_6), heptyl (C_7), octyl (C_8), nonyl (C_9), decyl (C_{10}), undecyl (C_{11}), dodecyl (C_{12}), tridecyl (C_{13}), tetradecyl (C_{14}), pentadecyl (C_{15}), and eicodecyl (C_{20}).

Examples of (unsubstituted) saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (amyl) (C_5), n-hexyl (C_6), and n-heptyl (C_7).

Examples of (unsubstituted) saturated branched alkyl groups include iso-propyl (C_3), iso-butyl (C_4), sec-butyl (C_4), tert-butyl (C_4), iso-pentyl (C_5), and neo-pentyl (C_5).

Cycloalkyl: The term "cycloalkyl," as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 3 to 7 ring atoms.

Examples of (unsubstituted) saturated cylcoalkyl groups include, but are not limited to, those derived from: cyclopropane (C_3), cyclobutane (C_4), cyclopentane (C_5), cyclohexane (C_6), cycloheptane (C_7), norbornane (C_7), norpinane (C_7), norcarane (C_7), adamantane (C_{10}), and decalin (decahydronaphthalene) (C_{10}).

Examples of (substituted) saturated cycloalkyl groups, which are also referred to herein as "alkyl-cycloalkyl" groups, include, but are not limited to, methylcyclopropyl, dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl, methylcyclopentyl, dimethylcyclopentyl, methylcyclohexyl, and dimethylcyclohexyl, menthane, thujane, carane, pinane, bornane, norcarane, and camphene.

Examples of (substituted) unsaturated cyclic alkenyl groups, which are also referred to herein as "alkyl-cycloalkenyl" groups, include, but are not limited to, methylcyclopropenyl,

dimethylcyclopropenyl, methylcyclobutenyl, dimethylcyclobutenyl, methylcyclopentenyl, dimethylcyclopentenyl, methylcyclohexenyl, and dimethylcyclohexenyl.

Examples of (substituted) cycloalkyl groups, with one or more other rings fused to the parent cycloalkyl group, include, but are not limited to, those derived from: indene (C_9), indan (e.g., 2,3-dihydro-1H-indene) (C_9), tetraline (1,2,3,4-tetrahydronaphthalene (C_{10}), acenaphthene (C_{12}), fluorene (C_{13}), phenalene (C_{13}), acephenanthrene (C_{15}), aceanthrene (C_{16}). For example, 2H-inden-2-yl is a C_5cycloalkyl group with a substituent (phenyl) fused thereto.

Alkenyl: The term "alkenyl," as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds. Examples of groups of alkenyl groups include C_{2-4}alkenyl, C_{2-7}alkenyl, C_{2-20}alkenyl.

Examples of (unsubstituted) unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, -CH=CH_2), 1-propenyl (-CH=CH-CH_3), 2-propenyl (allyl, -CH-CH=CH_2), isopropenyl (-C(CH_3)=CH_2), butenyl (C_4), pentenyl (C_5), and hexenyl (C_6).

Examples of (unsubstituted) unsaturated cyclic alkenyl groups, which are also referred to herein as "cycloalkenyl" groups, include, but are not limited to, cyclopropenyl (C_3), cyclobutenyl (C_4), cyclopentenyl (C_5), and cyclohexenyl (C_6).

Alkynyl: The term "alkynyl," as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds. Examples of groups of alkynyl groups include C_{2-4}alkynyl, C_{2-7}alkynyl, C_{2-20}alkynyl.

Examples of (unsubstituted) unsaturated alkynyl groups include, but are not limited to, ethynyl (ethinyl, -C≡CH) and 2-propynyl (propargyl, -CH_2-C≡CH).

Alkylidene: The term "alkylidene," as used herein, pertains to a divalent monodentate moiety obtained by removing two hydrogen atoms from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated. Examples of groups of alkylidene groups include C_{1-4}alkylidene, C_{1-7}alkylidene, C_{1-20}alkylidene.

Examples of alkylidene groups include, but are not limited to, methylidene (=CH_2), ethylidene (=CH-CH_3), vinylidene (=C=CH_2), and isopropylidene (=$C(CH_3)_2$). An example of a substituted alkylidene is benzylidene (=CH-Ph).

Alkylidyne: The term "alkylidyne," as used herein, pertains to a trivalent monodentate moiety obtained by removing three hydrogen atoms from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated. Examples of groups of alkylidyne groups include C_{1-4}alkylidyne, C_{1-7}alkylidyne, C_{1-20}alkylidyne.

Examples of alkylidyne groups include, but are not limited to, methylidyne (≡CH) and ethylidyne (≡C-CH_3).

Carbocyclyl: The term "carbocyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a carbocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 3 to 7 ring atoms.

In this context, the prefixes (e.g., C_{3-20}, C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms. For example, the term "C_{5-6}carbocyclyl," as used herein, pertains to a carbocyclyl group having 5 or 6 ring atoms. Examples of groups of carbocyclyl groups include C_{3-20}carbocyclyl, C_{3-10}carbocyclyl, C_{5-10}carbocyclyl, C_{3-7}carbocyclyl, and C_{5-7}carbocyclyl.

Examples of carbocyclic groups include, but are not limited to, those described above as cycloalkyl groups; and those described below as carboaryl groups.

Heterocyclyl: The term "heterocyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified), of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

In this context, the prefixes (e.g., C_{3-20}, C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the

term "C_{5-6}heterocyclyl," as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C_{3-20}heterocyclyl, C_{3-7}heterocyclyl, C_{5-7}heterocyclyl, and C_{5-6}heterocyclyl.

Examples of (non-aromatic) monocyclic heterocyclyl groups include, but are not limited to, those derived from:

N_1: aziridine (C_3), azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);

O_1: oxirane (C_3), oxetane (C_4), oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6), oxepin (C_7);

S_1: thiirane (C_3), thietane (C_4), thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6), thiepane (C_7);

O_2: dioxolane (C_5), dioxane (C_6), and dioxepane (C_7);

O_3: trioxane (C_6);

N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);

N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);

N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);

N_2O_1: oxadiazine (C_6);

O_1S_1: oxathiole (C_5) and oxathiane (thioxane) (C_6); and,

$N_1O_1S_1$: oxathiazine (C_6).

Examples of substituted (non-aromatic) monocyclic heterocyclyl groups include saccharides, in cyclic form, for example, furanoses (C_5), such as arabinofuranose, lyxofuranose, ribofuranose, and xylofuranse, and pyranoses (C_6), such as allopyranose, altropyranose, glucopyranose, mannopyranose, gulopyranose, idopyranose, galactopyranose, and talopyranose.

Examples of heterocyclyl groups which are also heteroaryl groups are described below with aryl groups.

Aryl: The term "aryl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 5 to 7 ring atoms.

In this context, the prefixes (e.g., C_{3-20}, C_{5-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6}aryl," as used herein, pertains to an aryl group having 5 or 6 ring atoms. Examples of groups of aryl groups include C_{3-20}aryl, C_{3-12}aryl, C_{5-12}aryl, C_{5-7}aryl, and C_{5-6}aryl.

The ring atoms may be all carbon atoms, as in "carboaryl groups" (e.g., C_{5-20}carboaryl).

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e., phenyl) (C_6), naphthalene (C_{10}), azulene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), naphthacene (C_{18}), and pyrene (C_{16}).

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indene (C_9), isoindene (C_9), and fluorene (C_{13}).

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups" (e.g., C_{5-20}heteroaryl).

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

N_1: pyrrole (azole) (C_5), pyridine (azine) (C_6);

O_1: furan (oxole) (C_5);

S_1: thiophene (thiole) (C_5);

N_1O_1: oxazole (C_5), isoxazole (C_5), isoxazine (C_6);

N_2O_1: oxadiazole (furazan) (C_5);

N_3O_1: oxatriazole (C_5);

N_1S_1: thiazole (C_5), isothiazole (C_5);

N_2: imidazole (1,3-diazole) (C_5), pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C_6);

N_3: triazole (C_5), triazine (C_6); and,

N_4: tetrazole (C_5).

Examples of heterocyclic groups (some of which are also heteroaryl groups) which comprise fused rings, include, but are not limited to:

C_9heterocyclic groups (with 2 fused rings) derived from benzofuran (O_1), isobenzofuran (O_1), indole (N_1), isoindole (N_1), indolizine (N_1), indoline (N_1), isoindoline (N_1), purine (N_4) (e.g., adenine, guanine), benzimidazole (N_2), indazole (N_2), benzoxazole (N_1O_1), benzisoxazole (N_1O_1), benzodioxole (O_2), benzofurazan (N_2O_1), benzotriazole (N_3), benzothiofuran (S_1), benzothiazole (N_1S_1), benzothiadiazole (N_2S);

C_{10}heterocyclic groups (with 2 fused rings) derived from chromene (O_1), isochromene (O_1), chroman (O_1), isochroman (O_1), benzodioxan (O_2), quinoline (N_1), isoquinoline (N_1), quinolizine (N_1), benzoxazine (N_1O_1), benzodiazine (N_2), pyridopyridine (N_2), quinoxaline (N_2), quinazoline (N_2), cinnoline (N_2), phthalazine (N_2), naphthyridine (N_2), pteridine (N_4);

C_{13}heterocyclic groups (with 3 fused rings) derived from carbazole (N_1), dibenzofuran (O_1), dibenzothiophene (S_1), carboline (N_2), perimidine (N_2), pyridoindole (N_2); and,

C_{14}heterocyclic groups (with 3 fused rings) derived from acridine (N_1), xanthene (O_1), thioxanthene (S_1), oxanthrene (O_2), phenoxathiin (O_1S_1), phenazine (N_2), phenoxazine (N_1O_1), phenothiazine (N_1S_1), thianthrene (S_2), phenanthridine (N_1), phenanthroline (N_2), phenazine (N_2).

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -NH- group may be N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methypyrrole. Examples of N-substituents include, but are not limited to C_{1-7}alkyl, C_{3-20}heterocyclyl, C_{5-20}aryl, and acyl groups.

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -N= group may be substituted in the form of an N-oxide, that is, as -N(→O)= (also denoted -N^+(→O^-)=). For example, quinoline may be substituted to give quinoline N-oxide; pyridine to give pyridine N-oxide; benzofurazan to give benzofurazan N-oxide (also known as benzofuroxan).

Cyclic groups may additionally bear one or more oxo (=O) groups on ring carbon atoms. Monocyclic examples of such groups include, but are not limited to, those derived from:

C_5: cyclopentanone, cyclopentenone, cyclopentadienone;

C_6: cyclohexanone, cyclohexenone, cyclohexadienone;

O_1: furanone (C_5), pyrone (C_6);

N_1: pyrrolidone (pyrrolidinone) (C_5), piperidinone (piperidone) (C_6), piperidinedione (C_6);

N_2: imidazolidone (imidazolidinone) (C_5), pyrazolone (pyrazolinone) (C_5), piperazinone (C_6), piperazinedione (C_6), pyridazinone (C_6), pyrimidinone (C_6) (e.g., cytosine), pyrimidinedione (C_6) (e.g., thymine, uracil), barbituric acid (C_6);

N_1S_1: thiazolone (C_5), isothiazolone (C_5);

N_1O_1: oxazolinone (C_5).

Polycyclic examples of such groups include, but are not limited to, those derived from:

C_9: indenedione;

C_{10}: tetralone, decalone;

C_{14}: anthrone, phenanthrone;

N_1: oxindole (C_9);

O_1: benzopyrone (e.g., coumarin, isocoumarin, chromone) (C_{10});

N_1O_1: benzoxazolinone (C_9), benzoxazolinone (C_{10});

N_2: quinazolinedione (C_{10});

N_4: purinone (C_9) (e.g., guanine).

Still more examples of cyclic groups which bear one or more oxo (=O) groups on ring carbon atoms include, but are not limited to, those derived from:

cyclic anhydrides (-C(=O)-O-C(=O)- in a ring), including but not limited to maleic anhydride (C_5), succinic anhydride (C_5), and glutaric anhydride (C_6);

cyclic carbonates (-O-C(=O)-O- in a ring), such as ethylene carbonate (C_5) and 1,2-propylene carbonate (C_5);

imides (-C(=O)-NR-C(=O)- in a ring), including but not limited to, succinimide (C_5), maleimide (C_5), phthalimide, and glutarimide (C_6);

lactones (cyclic esters, -O-C(=O)- in a ring), including, but not limited to, β-propiolactone, γ-butyrolactone, δ-valerolactone (2-piperidone), and ε-caprolactone;

lactams (cyclic amides, -NR-C(=O)- in a ring), including, but not limited to, β-propiolactam (C_4), γ-butyrolactam (2-pyrrolidone) (C_5), δ-valerolactam (C_6), and ε-caprolactam (C_7);

cyclic carbamates (-O-C(=O)-NR- in a ring), such as 2-oxazolidone (C_5);

cyclic ureas (-NR-C(=O)-NR- in a ring), such as 2-imidazolidone (C_5) and pyrimidine-2,4-dione (e.g., thymine, uracil) (C_6).

The above alkyl, alkylidene, alkylidyne, heterocyclyl, and aryl groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the additional substituents listed below.

Hydrogen: -H. Note that if the substituent at a particular position is hydrogen, it may be convenient to refer to the compound as being "unsubstituted" at that position.

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C_{1-7}alkyl group (also referred to as a C_{1-7}alkoxy group, discussed below), a C_{3-20}heterocyclyl group (also referred to as a C_{3-20}heterocyclyloxy group), or a C_{5-20}aryl group (also referred to as a C_{5-20}aryloxy group), preferably a C_{1-7}alkyl group.

C_{1-7}alkoxy: -OR, wherein R is a C_{1-7}alkyl group. Examples of C_{1-7}alkoxy groups include, but are not limited to, -OMe (methoxy), -OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr) (isopropoxy), -O(nBu) (n-butoxy), -O(sBu) (sec-butoxy), -O(iBu) (isobutoxy), and -O(tBu) (tert-butoxy).

Acetal: -CH(OR^1)(OR^2), wherein R^1 and R^2 are independently acetal substituents, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group, or, in the case of a "cyclic" acetal group, R^1 and R^2, taken together with the two oxygen atoms to which they are attached, and the carbon atoms to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Examples of acetal groups include, but are not limited to, -CH($OMe)_2$, -CH($OEt)_2$, and -CH(OMe)(OEt).

Hemiacetal: -CH(OH)(OR^1), wherein R^1 is a hemiacetal substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of hemiacetal groups include, but are not limited to, -CH(OH)(OMe) and -CH(OH)(OEt).

Ketal: -CR(OR^1)(OR^2), where R^1 and R^2 are as defined for acetals, and R is a ketal substituent other than hydrogen, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples ketal groups include, but are not limited to, -C(Me)(OMe)$_2$, -C(Me)(OEt)$_2$, -C(Me)(OMe)(OEt), -C(Et)(OMe)$_2$, -C(Et)(OEt)$_2$, and -C(Et)(OMe)(OEt).

Hemiketal: -CR(OH)(OR^1), where R^1 is as defined for hemiacetals, and R is a hemiketal substituent other than hydrogen, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of hemiacetal groups include, but are not limited to, -C(Me)(OH)(OMe), -C(Et)(OH)(OMe), -C(Me)(OH)(OEt), and -C(Et)(OH)(OEt).

Oxo (keto, -one): =O.

Thione (thioketone): =S.

Imino (imine): =NR, wherein R is an imino substituent, for example, hydrogen, C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of ester groups include, but are not limited to, =NH, =NMe, =NEt, and =NPh.

Formyl (carbaldehyde, carboxaldehyde): -C(=O)H.

Acyl (keto): -C(=O)R, wherein R is an acyl substituent, for example, a C_{1-7}alkyl group (also referred to as C_{1-7}alkylacyl or C_{1-7}alkanoyl), a C_{3-20}heterocyclyl group (also referred to as C_{3-20}heterocyclylacyl), or a C_{5-20}aryl group (also referred to as C_{5-20}arylacyl), preferably a C_{1-7}alkyl group. Examples of acyl groups include, but are not limited to, -C(=O)CH$_3$ (acetyl), -C(=O)CH$_2$CH$_3$ (propionyl), -C(=O)C(CH$_3$)$_3$ (t-butyryl), and -C(=O)Ph (benzoyl, phenone).

mm; mobile phase acetonitrile - 0.1 M phosphate buffer (pH 2.5), 50:50; sample concentration 1.0 mg/ml; flow rate 1.5 mL/min; detector UV 220 nm.) Anal. Calcd. for $C_{20}H_{20}F_3N_3O_4S$ * 0.1EtOAc, %: C 52.78, H 4.52, N 9.05. Found, %: C 52.74, H 4.36, N 8.88.

Example 61

(E)-N-Hydroxy-3-(3-{[4-(3-nitrophenyl)-1-piperazinyl]sulfonyl}phenyl)-2-propenamide

(PX118893)

The title compound was obtained using methods analogous to those described above. M.p. 162 °C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 2.94-3.20 (4H, m); 3.45-3.69 (4H, m); 6.65 (lH, d, J=16.0 Hz); 7.02 (2H, d, J=9.0 Hz); 7.58 (lH, d, J= 16.0 Hz); 7.62-7.83 (2H, m); 7.84- 8.20 (4H, m); 10.20 (2H, br s). HPLC analysis on Omnisphere 5 C_{18}: impurities 2.0% (column size 4.6x150mm; mobile phase acetonitrile - 0.1 M phosphate buffer (pH 2.5), 40:60; sample concentration 0.3 mg/m1; flow rate 1.5 mL/min; detector UV 220 nm). Anal. Calcd. for $C_{19}H_{20}N_4O_6S$ containing 2.3% inorganic material, %: C 51.56, H 4.55, N 12.66. Found, %: C 51.54, H 4.50, N 12.57.

Example 62

(E)-N-Hydroxy-3-(3-{[4-(2-pyrimidinyl)-1-piperazinyl]sulfonyl}-phenyl)-2-propenamide

(PX118894)

The title compound was obtained using methods analogous to those described above. M.p. 200°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 2.78-3.15 (4H, m); 3.63-3.94 (4H, m); 6.58 (lH, d, J=16.0 Hz); 6.63 (lH, t, J=6.4 Hz); 7.56 (lH, d, J= 16.0 Hz); 7.57-8.12 (4H, m); 8.34 (2H, d, J=6.4 Hz); 9.16 (lH, br s); 10.80 ppm (lH, br s). HPLC analysis on Alltima C_{18}: impurities 4.8% (column size: 4.6x150 mm; mobile phase acetonitrile - 0.1 M phosphate buffer (pH 2.5), 30:70; sample concentration 1.0 mg/ml; flow rate 1.15 mL/min; detector UV 254 nm.) Anal. Calcd for $C_{17}H_{19}N_5O_4S$, %: C 52.43, H 4.92, N 17.98. Found, %: C 52.37, H 4.89, N 17.69.

Example 63

(E)-3-(3-{[4-(2,2-Diphenylethyl)-l-piperazinyl]sulfonyl}phenyl)-N-hydroxy-2-propenamide

(PX118913)

The title compound was obtained using methods analogous to those described above. M.p. 117°C (decomposes). ^{1}H NMR (DMSO-d_6, HMDSO), δ: 2.42-2.62 (4H, m, overlapped with a signal of DMSO); 2.70-2.87 (4H, m); 2.92 (2H, d, J=7.3 Hz); 4.18 (lH t, J= 7.3 Hz); 6.58 (lH, d, J=15.8 Hz); 7.02-7.35 (10H, m); 7.53 (lH, d, J= 15.8 Hz); 7.61-7.70 (2H, m); 7.80-7.92 (2H, m); 9.14 (lH, br s); 10.80 ppm (lH, br s). HPLC analysis on Omnisphere C_{18}: impurities 4.5% (column size 4.6x150 mm; mobile phase acetonitrile - 0.1 M phosphate buffer (pH 2.5), 40:60; sample concentration 0.5 mg/ml; flow rate: 1.2 mL/min; detector UV 220 nm.) Anal. Calcd. for $C_{27}H_{29}N_3O_4S$ * 0.2 M Et_2O containing 1.8% of inorganic impurities, %: C 64.75, H 6.06, N 8.15. Found, %: C 64.76, H 6.07, N 8.19.

Example 64

(E)-N-Hydroxy-3-[3-({4-[2-(2naphthyl)ethyl]-1-piperazinyl}sulfonyl)phenyl]-2-propenamide

(PX118914)

The title compound was obtained using methods analogous to those described above. M.p. 184°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 2.38-3.07 (12H, m, partly overlapped with a signal ofDMSO); 6.63 (lH, d, J=16.0 Hz); 7.20-7.54 (4H, m); 7.57-7.98 (8H, m); 9.16 (lH, br s); 10.78 ppm (lH, br s). HPLC analysis on Alltima C_{18}: impurities 1.0% (column size 4.6x150mm; mobile phase acetonitrile - 0.1 M phosphate buffer (pH 2.5), 35:65; sample concentration 1.0 mg/ml; flow rate 1.2 mL/min; detector UV 220 nm). Anal. Calcd. for $C_{25}H_{27}N_3O_4S$, %: C 64.50, H 5.85, N 9.03. Found, %: C 64.34, H 5.74, N 9.02.

Example 65

3-(4-Chlorosulfonylphenyl)acrylic acid (8)

To neat chlorosulfonic acid (26.5 mL, 0.4 mol) at 18°C temperature slowly cinnamic acid (7) (7.35 g, 0.05 mol) was added. As the reaction proceeded, hydrogen chloride gas evolved. The reaction mixture was stirred successively at 20°C for 3 hours and at 42°C for 3 hours. The dark, viscous syrup was poured into ice water, and the precipitated solid was filtered and washed with water. The title compound was obtained (6.8 g, 55%) as a white solid. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 6.55 (1H, d, J=16.0 Hz); 7.58 (1H, d, J=16.0 Hz); 7.65 (4H, s); 8.15 (1H, br s).

Example 66

(E)-3-[4-({4-[3-(Trifluoromethyl)phenyl]-1-piperazinyl}sulfonyl)phenyl]-2-propenoic acid (9a)

To a suspension of 1-(α,α,α-trifluoro-m-tolyl)piperazine hydrochloride (0.43 g, 1.62 mmol) in dioxane (5 mL) a solution of $NaHCO_3$ (0.27 g, 3.24 mmol) in water (4 mL) and a solution of 3-(4-chlorosulfonyl-phenyl)-acrylic acid (8) (0.40 g, 1.62 mmol) were added and the resultant mixture was stirred at ambient temperature for 20 hours. The reaction mixture was poured into water (50 mL) and the pH of the medium was brought to ~4 with 2 N HCl. The precipitated solid was filtered, washed with water, and dried in vacuum to give the title compound (0.59 g, 82%). ^{1}H NMR (DMSO-d_6, HMDSO), δ: 2.96-3.67 (8H, m, overlapped with a signal of water); 6.74 (1H, d, J=16.3 Hz); 7.01-7.57 (4H, m); 7.67 (1H, d, J=16.3 Hz); 7.82 (2H, d, J=8.4 Hz); 8.00 (2H, d, J=8.4 Hz); 12.71 (1H, br s).

Example 67

(E)-3-[4-({4-[Bis(4-fluorophenyl)methyl]-1-piperazinyl}sulfonyl)phenyl]-2-propenoic acid (9b)

To a suspension of 1-bis(4-fluorophenyl)methyl piperazine (0.47 g, 1.62 mmol) in dioxane (5 mL) a solution of $NaHCO_3$ (0.27 g, 3.24 mmol) in water (4 mL) and a solution of 3-(4-chlorosulfonyl-phenyl)-acrylic acid (8) (0.40 g, 1.62 mmol) were added and the resultant mixture was stirred at ambient temperature for 20 hours. The reaction mixture was poured into water (50 mL), the pH of the medium was brought to ~4 with 2 N HCl, and extracted with ethyl acetate. The extract was washed successively with water, brine, and dried (Na_2SO_4). The solvent was removed and the crude product was crystallized from dioxane to give the title compound (0.58 g, 63%) as a white solid. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 2.19-2.50 (4H, m, overlapped with a signal of DMSO); 2.80-3.12 (4H, m); 4.42 (1H, s); 6.78 (1H, d, J=16.0 Hz); 7.11 (4H, t, J=9.0 Hz); 7.41 (4H, dd, J=8.6 and 5.6 Hz); 7.72 (1H, d, J=16.0 Hz); 7.78 (2H, d, J=8.2 Hz); 8.00 (2H, d, J=8.2 Hz); 12.68 (1H, br s).

Example 68

(E)-3-[4-({4-[3-(Trifluoromethyl)phenyl]-1-piperazinyl}sulfonyl)phenyl]-2-propenoyl chloride (**10a**)

To a suspension of (E)-3-[4-({4-[3-(trifluoromethyl)phenyl]-1-piperazinyl}sulfonyl)phenyl]-2-propenoic acid (**9a**) (0.30 g, 0.69 mmol) in dichloromethane (7 mL) oxalyl chloride (0.2 mL, 2.4 mmol) and a drop of dimethylformamide were added. The reaction mixture was stirred at ambient temperature for 0.5 hours and at 42°C for 1 hour. The reaction mixture was evaporated and the residue was dried in vacuum to give (E)-3-[4-({4-[3-(trifluoromethyl)phenyl]-1-piperazinyl}sulfonyl)phenyl]-2-propenoyl chloride (**10a**) (0.31 g) in a form of a crude product.

Example 69

(E)-3-[4-({4-[Bis(4-fluorophenyl)methyl]-1-piperazinyl}sulfonyl)phenyl]-2-propenoyl chloride (**10b**)

To a solution of (E)-3-[4-({4-[bis(4-fluorophenyl)methyl]-1-piperazinyl}sulfonyl)phenyl]-2-propenoic acid (**9b**) (0.25 g,0.5 mmol) in dichloromethane (7 mL) oxalyl chloride (0.15 mL, 1.75 mmol) and a drop of dimethylformamide were added. The reaction mixture was stirred at ambient temperature for 1 hour, then the mixture was evaporated and the residue was dried in vacuum to give (E)-3-[4-({4-[bis(4-fluorophenyl)methyl]-1-piperazinyl}sulfonyl)phenyl]-2-propenoyl chloride (**10b**) (0.26 g) in a form of a crude product.

Example 70

(E)-N-Hydroxy-3-[4-({4-[3-(trifluoromethyl)phenyl]-1-piperazinyl}-sulfonyl)phenyl]-2-propenamide (**PX118937**)

To a suspension of hydroxylamine hydrochloride (0.24 g, 3.4 mmol) in tetrahydrofuran (5.0 mL) a solution of $NaHCO_3$ (0.40 g, 4.8 mmol) in water (6 mL) was added and the resultant mixture was stirred at ambient temperature for 5 minutes. The reaction mixture was added to a suspension of (E)-3-[4-({4-[3-(trifluoromethyl)phenyl]-1-piperazinyl}sulfonyl)phenyl]-2-propenoyl chloride (**10a**) (0.31 g) in tetrahydrofuran (5 mL) and the mixture was stirred at ambient temperature for 0.5 hours. The mixture was poured into water (25 mL), the precipitate was filtered, washed with water, ether, and dried to give the title compound (0.23 g, 73%). M.p. 178-179°C. ^{1}H NMR (DMSO-d_6,

HMDSO), δ: 2.95-3.10 (4H, m); 3.23-3.40 (4H, m, overlapped with a signal of water); 6.62 (1H, d, J=15.9 Hz); 7.09 (1H, d, J=7.7 Hz); 7.16 (1H, s); 7.19 (1H, d, J=8.0 Hz); 7.40 (1H, t, J=7.7 Hz); 7.54 (1H, d, J=15.9 Hz); 7.80 (2H, d, J=8.4 Hz); 7.83 (2H, d, J=8.4 Hz); 9.35 (1H, br s); 10.72 (1H, br s). HPLC analysis on Omnispher 5 C_{18} column: impurities 3.5% (column size 4.6x150 mm; mobile phase acetonitrile - 0.1M acetate buffer (pH 5.0), 50:50; sample concentration 1 mg/ml; flow rate 1.3 mL/min; detector UV 254 nm). Anal. Calcd for $C_{20}H_{20}F_3N_3O_4S$, %: C 52.74, H 4.43, N 9.23, S 7.04. Found, %: C 52.04, H 4.29, N 8.86, S 7.20.

Example 71

(E)-3-[4-({4-[Bis(4-fluorophenyl)methyl]-1-piperazinyl}sulfonyl)phenyl]-N-hydroxy-2-propenamide (**PX118965**)

To a suspension of hydroxylamine hydrochloride (0.18 g, 2.5 mmol) in tetrahydrofuran (5.0 mL) a solution of $NaHCO_3$ (0.30 g, 3.5 mmol) in water (5 mL) was added and the resultant mixture was stirred at ambient temperature for 5 minutes. The reaction mixture was added to a solution of (E)-3-[4-({4-[bis(4-fluorophenyl)methyl]-1-piperazinyl}sulfonyl)phenyl]-2-propenoyl chloride (**10b**) (0.26 g) in tetrahydrofuran (5 mL) and the obtained mixture was stirred at ambient temperature for 0.5 hours. The mixture was poured into water (25 mL), extracted with ethyl acetate, the extract was washed with water, brine, and dried (Na_2SO_4). The solvent was removed and the residue was chromatographed on silica gel with chloroform - isopropanol (9:1) as eluent to give the title compound (0.087 g, 34%). M.p. 125-126°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 2.26-2.42 (4H, m); 2.81-3.00 (4H, m); 4.39 (1H, s); 6.64 (1H, d, J=15.8 Hz); 7.07 (4H, t, J=8.6 Hz); 7.37 (4H, dd, J=8.4 and 5.6 Hz); 7.57 (1H, d, J=15.8 Hz); 7.74 (2H, d, J=8.0 Hz); 7.83 (2H, d, J=8.0 Hz); 9.19 (1H, s); 10.93 (1H, s). HPLC analysis on Alltima C_{18} column: impurities 2% (column size 4.6x150 mm; mobile phase acetonitrile - 0.1M phosphate buffer (pH 2.5), 70:30; sample concentration 1.0 mg/ml; flow rate 1.0 mL/min; detector: UV 215 nm). Anal. Calcd for $C_{26}H_{25}F_2N_3O_4S * 0.3\ Et_2O * 0.2$ iso-PrOH $* 0.1\ CHCl_3$ (an exhaustively dried material contains all the indicated traces of solvents (PMR)), %: C 59.87, H 5.35, N 7.51, S 5.73. Found, %: C 59.85, H 5.36, N 7.29, S 5.60.

Example 72

1-(1,3-Benzodioxol-5-ylmethyl)-4-({-[(E)-3-(hydroxyamino)-3-oxo-1-propenyl]phenyl}sulfonyl)piperazin-1-ium dihydrogen phosphate (**PX118882**)

The title compound was obtained using methods analogous to those described above. M.p. 210-211 °C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 2.30-2.45 (4H, m, overlapped with a signal of DMSO); 2.82-2.96 (4H, m); 3.36 (2H, s); 3.89-4.67 (br s, interchangeable protons); 5.95 (2H, s); 6.62 (lH, d, J=15.8 Hz); 6.68 (lH, d, J=7.8 Hz); 6.77 (lH, s); 6.79 (lH, d, J=7.8 Hz); 7.53 (2H, d, J=15.8 Hz); 7.73 (2H, d, J=8.0 Hz), 7.81 (2H, d, J=8.0 Hz). HPLC analysis on Omnispher 5 C_{18} : impurities 2.5% (column size 4.6x150mm; mobile phase acetonitrile - 0.1M phosphate buffer (pH 2.5), 20:80; sample concentration 0.5 mg/ml; flow rate 1.5 ml/min; detector UV 220 nm). Anal. Calcd. for $C_{21}H_{23}N_3O_6S * H_3PO_4 * 0.25\ NaH_2PO_4$, %: C 43.98, H 4.66, N 7.33, S 5.59. Found, %: C 43.59, H 4.75, N 7.50, S 5.70.

Example 73

(E)-N-Hydroxy-3-(4-{[4-(4-nitorphenyl)-1-piperazinyl]sulfonyl}phenyl)-2-propenamide (**PX118918**)

The title compound was obtained using methods analogous to those described above. M. p. 199-200°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 2.97-3.09 (4H, m); 3.49-3.62 (4H, m); 6.61 (1H, d, J=15.7 Hz); 6.99 (2H, d, J=9.2 Hz); 7.52 (1H, d, J=15. 7 Hz); 7.78 (2H, d, J=9.0 Hz); 7.81 (2H, d, J=9.0 Hz); 8.02 (2H, d, J=9.2 Hz); 9.17 (1H, s); 10.91 (1H, s). HPLC analysis on Omnispher 5 C_{18}: impurities 3.0% (column size 4.6x150mm; mobile phase acetonitrile - 0.1M phosphate buffer (pH 2.5), 40:60; sample concentration 0.25 mg/ml; flow rate 1.5 mL/min; detector UV 270 nm). Anal. Calcd. for $C_{19}H_{20}N_4O_6S$, %: C 52.77, H 4.66, N 12.96, S 7.41. Found, %: C 52.56, H 4.74, N 12.41, S 7.28.

Example 74

(E)-3-(4-{[4-(2-Fluorophenyl)-1-piperazinyl]sulfonyl}phenyl)-N-hydroxy-2-propenamide (**PX118891**)

The title compound was obtained using methods analogous to those described above. M. p. 196-197°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 3.00-3.14 (8H, m); 6.63 (lH, d, J=15.8 Hz); 6.92- 7.18 (4H, m); 7.55 (lH, d, J=15.8 Hz); 7.80 (2H, d, J=8.6 Hz); 7.84 (2H, d, J=8.6 Hz); 9.16 (lH, s); 10.92 (lH, s). HPLC analysis on Alltima C_{18} : impurities 3.5% (column size

4.6x150mm; mobile phase acetonitrile - 0.1M phosphate buffer (pH 2.5), 50:50; sample concentration 1.0 mg/ml; flow rate 1.0 mL/min; detector UV 254 nm.) Anal. Calcd. for $C_{19}H_{20}FN_3O_4S$ * 0.2 EtOAc, %: C 56.21, H 5.15, N 9.93, S 7.58. Found, %: C 56.07, H 5.10, N 9.97, S 7.60.

Example 75

(E)-N-Hydroxy-3-(4-{[4-(3-methoxyphenyl)-1-piperazinyl]sulfonyl}phenyl)-2-propenamide

(PX118892)

The title compound was obtained using methods analogous to those described above. M. p. 199-200°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 2.95-3.06 (4H, m); 3.13-3.25 (4H, m); 3.68 (3H, s); 6.38 (IH, d, J=8.0 Hz); 6.42 (IH, s); 6.47 (IH, d, J=8.2 Hz); 6.61 (IH, d, J=16.0 Hz); 7.09 (IH, t, J=8.0 Hz); 7.54 (IH, d, J=16.0 Hz); 7.78 (2H, d, J=8.4 Hz); 7.83 (2H, d, J=8.4 Hz); 9.17 (IH, s); 10.91 (IH, br s). HPLC analysis on Omnispher 5 C_{18}: impurities 4.5% (column size 4.6x150mm; mobile phase acetonitrile - 0.1M phosphate buffer (pH 2.5), 45:55; sample concentration 0.15 mg/ml; flow rate 1.2 mL/min; detector UV 254 nm). Anal. Calcd. for $C_{20}H_{23}N_3O_5S$ * 0.1 EtOAc * 0.2 H_2O, %: C 57.00, H 5.67, N 9.77, S 7.46. Found, %: C 57.04, H 5.52, N 9.64, S 7.38 .

Example 76

(E)-N-Hydroxy-3-(4-{[4-(2-methoxyphenyl)-1-piperazinyl]sulfonyl}phenyl)-2-propenamide

(PX118905)

The title compound was obtained using methods analogous to those described above. M. p. 225-226°C. $_1$H NMR (DMSO-d_6, HMDSO) δ: 2.89-3.13 (8H, m); 3.70 (3H, s); 6.63 (IH, d, J=15.8 Hz); 6.83-7.00 (4H, m); 7.56 (IH, d, J=15.8 Hz); 7.80 (2H, d, J=8.2 Hz); 7.85 (2H, d, J=8.2 Hz); 9.18 (IH, br s); 10.93 (IH, br s). HPLC analysis on Omnispher 5 C_{18}: impurities 4.5%. (column size 4.6x150mm; mobile phase acetonitrile - 0.1M phosphate buffer (pH 2.5), 40:60; sample concentration 0.2 mg/ml; flow rate 1.2 mL/min; detector UV 254 nm). Anal. Calcd. for $C_{20}H_{23}N_3O_6S$ * 0.2 EtOAc * 0.2 H_2O, %: C 56.95, H 5.74, N 9.58, S 7.31. Found, %: C 56.95, H 5.66, N 9.40, S 7.54.

Example 77

3-{4-[4-(3-Chloro-phenyl)-piperazine-1-sulfonyl]-phenyl}-N-hydroxy-acrylamide **(PX118906)**

The title compound was obtained using methods analogous to those described above.

Example 78

N-Hydroxy-3-[4-(4-pyrimidin-2-yl-piperazine-1-sulfonyl)-phenyl]-acrylamide **(PX118907)**

The title compound was obtained using methods analogous to those described above.

Example 79

3-[4-(4-Benzhydryl-piperazine-1-sulfonyl)-phenyl-N-hydroxy-acrylamide **(PX118910)**

The title compound was obtained using methods analogous to those described above.

Example 80

N-Hydroxy-3-[4-(3-methyl-4-m-tolyl-piperazine-1-sulfonyl)-phenyl]-acrylamide **(PX118911)**

The title compound was obtained using methods analogous to those described above.

Method E - General Synthesis of 1-Acylpiperazines

Appropriate carboxylic acid (1-2 mmol) and hydroxybenztriazole (1 eq) were suspended in chloroform (2 mL/1 mmol) and a solution of 1,3-dicylcohexylcarbodiimide (DCC) (1 eq) in a minimal amount of dimethylformamide was added. The mixture was stirred for 30 minutes at room temperature to give white suspension. The mixture was transferred slowly to a pre-cooled solution of anhydrous piperazine (5 eq) in chloroform (1 mL/1 mmol). The reaction was stirred for 4 hours at room temperature, the white suspension (DCU) was filtered, and the filtrate was extracted with 2 M HCl. The HCl extracts were basified with 2 M NaOH to pH 9, extracted with ethyl acetate, and the organic extract was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was used without further purification, or was purified on silica gel (20 g) with methanol-NH_4OH (ca. 95:5 to 90:10) as eluent.

Example 81

2-Naphthyl(1-piperazinyl)methanone (13a)

The title compound was prepared from naphthalene 2-carboxylic acid (12a), using Method E, yield 94%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.92(s, 1H); 2.87(t, J=5.0 Hz, 4H); 3.63(t, J=5.0 Hz, 4H); 7.43-7.74(m, 3H); 7.89-8.12(m, 4H).

Example 82

2-(5-Methoxy-1H-indol-3-yl)-1-(1-piperazinyl)-1-ethanone (13b)

The title compound was prepared from 2-(5-methoxy-1H-indol-3-yl)acetic acid (12b), using Method E, yield 75%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.61(s, 1H); 2.63(t, J=5.0 Hz, 2H); 2.78(t, J=5.0 Hz, 2H); 3.45(t, J=5.0 Hz, 2H); 3.65(t, J=5.0 Hz, 2H); 3.78(s, 2H); 3.83(s, 3H); 6.78(dd, J=8.8 and 3.0 Hz, 1H); 7.06(t, J= 3.0 Hz, 2H); 7.22(d, J=8.8 Hz, 1H); 8.27(s, 1H).

Example 83

2-(2-Naphthyloxy)-1-(1-piperazinyl)-1-ethanone (13c)

The title compound was prepared from 2-(2-naphthyloxy)acetic acid (2c), using Method E, yield 97%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.69(s, 1H); 2.83(t, J=5.0 Hz, 4H); 3.61(t, J=5.0 Hz, 4H); 4.81(s, 2H); 7.12-7.58(m, 4H); 7.69-7.92(m, 3H).

Example 84

2-(1-Naphthyloxy)-1-(1-piperazinyl)-1-ethanone (13d)

The title compound was prepared from 2-(1-naphthyloxy)acetic acid (2d), using Method E, yield 82%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.87(s, 1H); 2.63(t, J=5.0 Hz, 2H); 2.83(t, J=5.0 Hz, 2H); 3.45(t, J=5.0 Hz, 2H); 3.65(t, J=5.0 Hz, 2H); 3.89(s, 2H); 7.29-7.61(m, 3H); 7.65-7.96(m, 4H).

Example 85

2-(1-Benzothiophen-3-yl)-1-(1-piperazinyl)-1-ethanone (13e)

The title compound was prepared from 2-(1-benzothiophen-3-yl)acetic acid (12e), using Method E, yield 92%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.61(s, 1H); 2.67(t, J=5.0 Hz, 2H);

2.83(t, J=5.0 Hz, 2H); 3.43(t, J=5.0 Hz, 2H); 3.67(t, J=5.0 Hz, 2H); 3.81(s, 2H); 7.21-7.54(m, 3H); 7.69-7.98(m, 2H).

Example 86

3-(1H-Indol-3-yl)-1-(1-piperazinyl)-1-propanone (**13f**)

The title compound was prepared from 3-(1H-indol-3-yl)propanoic acid (**12f**), using Method E, yield 79%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 2.03(s, 1H); 2.54-2.89(m, 6H); 3.03-3.21(m, 2H); 3.34(t, J=5.0 Hz, 2H); 3.58(t, J=5.0 Hz, 2H); 7.00-7.45(m, 4H); 7.52-7.74(m, 1H); 8.13(bs, 1H).

Example 87

1H-Indol-3-yl(1-piperazinyl)methanone (**13g**)

The title compound was prepared from 1H-indole-3-carboxylic acid (**12g**), using Method E, yield 39%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.67(s, 1H); 2.89(t, J=5.0 Hz, 4H); 3.69(t, J=5.0 Hz, 4H); 7.09-7.43(m, 4H); 7.63-7.87(m, 1H); 9.27(bs, 1H).

Example 88

Tert-butyl 4-benzoyl-1-piperazinecarboxylate (**15h**)

To a solution of N-Boc-piperazine (**14**) (1.00 g, 5.37 mmol) in dioxane (5 mL), a solution of NaOH (0.50 g, 12.9 mmol) in water (5 mL) followed by a solution of benzoyl chloride (0.75 mL, 6.44 mmol) in dioxane (2 mL) under vigorous stirring were added. The reaction mixture was stirred at ambient temperature for 4 hours, diluted with brine (20 mL), and extracted with ethyl acetate (2 x 25 mL). The organic extract was washed successively with brine (20 mL), saturated $NaHCO_3$ (20 mL), saturated KH_2PO_4 (20 mL), and dried (Na_2SO_4). The solvents were evaporated to give the title compound (1.400 g, 90%) which was used in the next step of the synthesis without further purification. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.41(s, 9H), 2.86(t, J=5.0 Hz, 4H); 3.62(t, J=5.0 Hz, 4H); 7.34(s, 5H).

Method F - General Synthesis of Tert-Butyl 1-Piperazinecarboxylates

A solution of appropriate acid **12i-k** (2.75 mmol) in anhydrous dimethylformamide (4.5 mL) was cooled in ice bath under argon and carbonyldiimidazole (0.490 g, 3.01 mmol) was added. The mixture was stirred for 30 minutes, then a solution of N-Boc-piperazine

14 (2.75 mmol) in dimethylformamide (3 mL) was added. The mixture was stirred at ice bath temperature for 1 hour, followed by 20 hours at room temperature, diluted with brine (20 mL), and extracted with ethyl acetate (3 x 25 mL). The organic phase was washed successively with brine (20 mL), saturated KH_2PO_4 (20 mL), brine (20 mL), and dried (Na_2SO_4). The solvent was evaporated and the crude product was used in a further step of the synthesis without additional purification, or was purified on silica gel (20 g) with ethyl acetate as eluent.

Example 89

tert-Butyl 4-[4-(dimethylamino)benzoyl]-1-piperazinecarboxylate (15i)

The title compound was prepared from 4-(dimethylamino)benzoic acid (12i), using Method F, yield 61%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.45(s, 9H); 2.98(s, 6H); 3.29-3.74(m, 8H); 6.69(d, J=8.8 Hz, 2H); 7.36(d, J=8.8 Hz, 2H).

Example 90

tert-Butyl 4-(4-cyanobenzoyl)-1-piperazinecarboxylate (15j)

The title compound was prepared from 4-cyanobenzoic acid (12j), using Method F, yield 96%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.40(s, 9H); 2.87(t, J=5.0 Hz, 4H); 3.63(t, J=5.0 Hz, 4H); 6.70(d, J=8.8 Hz, 2H); 7.12(d, J=8.8 Hz, 2H).

Example 91

tert-Butyl 4-{2-[4-(dimethylamino)phenyl]acetyl}-1-piperazinecarboxylate (15k)

The title compound was prepared from 2-[4-(dimethylamino)phenyl]acetic acid (12k), using Method F, yield 60%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.43(s, 9H); 2.92(s, 6H); 3.07-3.78(m, 8H); 3.65(s, 2H); 6.72(d, J=8.8 Hz, 2H); 7.14(d, J=8.8 Hz, 2H).

Method G - General Synthesis of 1-Acylpiperazines

A solution of an appropriate N-Boc-piperazine derivative 15h-k (2.5 mmol) in 1 N HCl methanol (12.5 mL) (made in situ from AcCl and MeOH) was stirred for 2 hours at ambient temperature, and then the mixture was evaporated. To the residue, water (30 mL) was added, the mixture was washed with diethyl ether, and the pH of the aqueous phase was brought to 9 with 2 M NaOH. The reaction product was extracted with

chloroform (3 x 25 mL), the organic extract was washed with brine (25 mL), and dried (Na_2SO_4). The solvent was evaporated and the crude product was used in a further step of the synthesis without additional purification, or was purified on silica gel (20 g) with methanol-NH_4OH (9:1) as eluent.

Example 92

Phenyl(1-piperazinyl)methanone (**13h**)

The title compound was prepared from tert-butyl 4-benzoyl-1-piperazinecarboxylate (**15h**), using Method G, yield 87%. ^1H NMR ($CDCl_3$, HMDS), δ: 1.81(s, 1H); 2.76(t, J=5.0 Hz, 4H); 3.56(bs, 4H); 7.41(s, 5H).

Example 93

[4-(Dimethylamino)phenyl](1-piperazinyl)methanone (**13i**)

The title compound was prepared from tert-butyl 4-[4-(dimethylamino)benzoyl]-1-piperazinecarboxylate (**15i**), using Method G, yield 82%. ^1H NMR ($CDCl_3$, HMDS), δ: 1.91(s, 1H); 2.87(t, J=5.0 Hz, 4H); 2.98(s, 6H); 3.63(t, J=5.0 Hz, 4H); 6.67(d, J=8.8 Hz, 2H); 7.34(d, J=8.8 Hz, 2H).

Example 94

4-(1-Piperazinylcarbonyl)benzonitrile (**13j**)

The title compound was prepared from tert-butyl 4-(4-cyanobenzoyl)-1-piperazinecarboxylate (**15j**), using Method G, yield 62%. ^1H NMR ($CDCl_3$, HMDS), δ: 1.92(s, 1H); 2.69-3.02(m, 4H); 3.14-3.92(m, 4H); 7.49(d, J=8.8 Hz, 2H); 7.72(d, J=8.8 Hz, 2H).

Example 95

8-(4-{2-[4-(Dimethylamino)phenyl]acetyl}-1-piperazinyl)-N-hydroxy-8-oxooctanamide (**13k**)

The title compound was prepared from tert-butyl 4-{2-[4-(dimethylamino)phenyl]acetyl}-1-piperazinecarboxylate (**15k**), using Method G, yield 80%. ^1H NMR ($CDCl_3$, HMDS), δ: 1.63(s, 1H); 2.63(t, J=5.0 Hz, 2H); 2.78(t, J=5.0 Hz, 2H); 2.92(s, 6H); 3.41(t, J=5.0 Hz, 2H); 3.58(t, J=5.0 Hz, 2H); 3.65(s, 2H); 6.99(d, J=8.8 Hz, 2H); 7.11(d, J=8.8 Hz, 2H).

Method H - General Synthesis of N-Monosubstituted Piperazines

To a suspension of $LiAlH_4$ (2.5 eq) in anhydrous tetrahydrofuran (2-3 mL/1 mmol) under argon atmosphere, a solution of appropriate N-acylpiperazine 13b,c,f,g,k (1 eq) in tetrahydrofuran (1.5 mL/1 mmol) was added, and the mixture was stirred at reflux temperature until the initial compound disappeared (3-7 hours on average). The reaction mixture was allowed to cool to room temperature and methanol, water, and 1N NaOH were carefully added. The reaction mixture was stirred for 2 hours at room temperature and the mixture passed through a celite pad. The filtrate was evaporated and the residue was purified on silica gel (20 g) with methanol-NH_4OH (9:1) as eluent to give the expected piperazine product.

Example 96

5-Methoxy-3-[2-(1-piperazinyl)ethyl]-1H-indole (**16b**)

The title compound was prepared from 2-(5-methoxy-1H-indol-3-yl)-1-(1-piperazinyl)-1-ethanone (**13b**), using Method H, yield 38%. ^1H NMR ($CDCl_3$, HMDS), δ: 1.61(s, 1H); 2.47-2.81(m, 6H); 2.87-3.09(m, 6H); 3.85(s, 3H); 6.85(dd, J=8.8 and 3.0 Hz, 1H); 7.05(t, J= 3.0 Hz, 2H); 7.25(d, J=8.8 Hz, 1H); 7.83(s, 1H).

Example 97

1-[2-(2-Naphthyloxy)ethyl]piperazine (**16c**)

The title compound was prepared from 2-(2-naphthyloxy)-1-(1-piperazinyl)-1-ethanone (**13c**), using Method H, yield 43%. ^1H NMR ($CDCl_3$, HMDS), δ: 1.48(s, 1H); 2.56(t, J=5.0 Hz, 4H); 2.85(t, J=6.0 Hz, 2H); 2.92(t, J=5.0 Hz, 4H); 4.25(t, J=6.0 Hz, 2H); 7.05-7.58(m, 4H); 7.65-7.89(m, 3H).

Example 98

3-[3-(1-Piperazinyl)propyl]-1H-indole (**16f**)

The title compound was prepared from 3-(1H-indol-3-yl)-1-(1-piperazinyl)-1-propanone (**13f**), using Method H, yield 74%. ^1H NMR (DMSO, HMDS), δ: 1.69(t, J=7.0 Hz, 1H); 1.78(t, J=7.0 Hz, 1H); 2.12-2.34(m, 6H); 2.36-2.47(1H, overlapped with DMSO signal); 2.49-2.76(m, 6H); 6.67-7.00(m, 3H); 7.05-7.45(m, 2H); 10.49(s, 1H).

Example 99

3-(1-Piperazinylmethyl)-1H-indole (16g)

The title compound was prepared from 1H-indol-3-yl(1-piperazinyl)methanone (13g), using Method H, yield 63%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.81(s, 1H); 2.49(t, J=5.0 Hz, 4H); 2.89(t, J=5.0 Hz, 4H); 3.72(s, 2H); 7.05-7.52(m, 4H); 7.65-7.83(m, 1H); 8.14(bs, 1H).

Example 100

N,N-Dimethyl-4-[2-(1-piperazinyl)ethyl]aniline (16k)

The title compound was prepared from 8-(4-{2-[4-(dimethylamino)phenyl] acetyl}-1-piperazinyl)-N-hydroxy-8-oxooctanamide (13k), using Method H, yield 82%. ^{1}H NMR ($CDCl_3$, HMDS), δ: 1.74(s, 1H); 2.34-2.72(m, 8H); 2.89(s, 6H); 2.81-3.03(m, 4H); 6.72(d, J=8.8 Hz, 2H); 7.09(d, J=8.8 Hz, 2H).

Method J - General Synthesis of Amidoesters

A solution of dicarbonic acid monoethyl (or monomethyl) ester 18a or 18b (2.73 mmol) in anhydrous tetrahydrofuran (5 mL) under argon atmosphere was cooled in an ice bath and to the solution carbonyldiimidazole (0.500 g, 3.08 mmol) was added. The mixture was stirred for 1 hour at ice bath temperature, then appropriate piperazine (2.73 mmol) was added. The reaction mixture was stirred at room temperature for 20 hours, concentrated under vacuum, and partitioned between brine (30 mL) and ethyl acetate (40 mL). The organic layer was washed successively with water (25 mL), 5% citric acid (25 mL), brine (25 mL), and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (20 g) with petroleum ether-ethyl acetate as eluent affording the corresponding reaction product.

Example 101

8-Oxo-8-(4-phenyl-piperazin-1-yl)-octanoic acid methyl ester (19a)

The title compound was obtained from suberic acid monomethyl ester (18b) and N-phenylpiperazine (17a) (commercially available) using Method J, yield 88%. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.05-1.72 (m, 8H); 2.02-2.30 (m, 8H); 3.30-3.60 (m, 4H); 3.51 (s, 3H); 7.21-7.51 (m, 5H).

Example 102

Ethyl 7-(4-benzhydryl-1-piperazinyl)-7-oxoheptanoate (**19b**)

The title compound was obtained from pimelic acid monoethyl ester (**18a**) and 1-(diphenylmethyl)piperazine (**17b**) (commercially available) using Method J, yield 80%. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.04-1.62 (m, 9H); 2.12-2.36 (m, 8H); 3.35-3.50 (m, 4H); 4.17 (q, 2H, J=7.3 Hz); 4.31 (s, 1H); 7.02-7.59 (m, 10H).

Example 103

Ethyl 7-oxo-7-(4-phenyl-1-piperazinyl)heptanoate (**19c**)

The title compound was obtained from pimelic acid monoethyl ester (**18a**) and N-phenylpiperazine (**17a**) (commercially available) using Method J, yield 88%. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.12-1.62 (m, 9H); 1.97-2.35 (m, 8H); 3.27-3.59 (m, 4H); 4.17 (q, 2H, J=7.2 Hz); 7.03-7.51 (m, 5H).

Example 104

Methyl 8-(4-benzhydryl-1-piperazinyl)-8-oxooctanoate (**19d**)

The title compound was obtained from suberic acid monomethyl ester (**18b**) and 1-(diphenylmethyl)piperazine (**17b**) (commercially available) using Method J, yield 91%. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.02-1.67 (m, 8H); 2.09-2.38 (m, 8H); 3.33-3.51 (m, 4H); 3.56 (s, 3H); 4.29 (s, 1H); 7.09-7.56 (m, 10H).

Example 105

Methyl 8-[4-(2-methoxyphenyl)-1-piperazinyl]-8-oxooctanoate (**19e**)

The title compound was obtained from suberic acid monomethyl ester (**18b**) and 1-(2-methoxyphenyl)piperazine hydrochloride (**17c**) (commercially available) (before the addition of hydrochloride (**17c**), triethylamine (3.0 mmol) was added to the reaction mixture), using Method J, yield 87%. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.12-1.60 (m, 8H); 1.97-2.82 (m, 8H, overlapped with a signal of DMSO); 3.40-3.62 (m, 7H); 3.75 (s, 3H); 6.92-7.15 (m, 4H).

Method K - General Synthesis of Amidoesters

To a solution of dicarbonic acid monoethyl (or monomethyl) ester **18a** or **18b** (2.75 mmol) in anhydrous dichloromethane (10 mL) oxalyl chloride (0.84 mL, 9.63 mmol) and a drop of dimethylformamide were added, and the resulting mixture was stirred for 30 minutes at room temperature followed by 1 hour at 40°C. The solution was carefully evaporated under reduced pressure and the residue was dried in vacuum at 40°C. The resulting chloride was dissolved in anhydrous tetrahydrofuran (3 mL) and the obtained solution to a cold suspension (ice bath) of piperazine (2.75 mmol), tetrahydrofuran (10 mL), and saturated $NaHCO_3$ (10 mL) under vigorous stirring was added. The stirring was continued for 1 hour at ice bath temperature and 20 hours at room temperature. The mixture was diluted with brine (30 mL) and extracted with ethyl acetate (3 x 25 mL). The organic phase was washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel (20 g) with benzene - ethyl acetate as eluent to give the corresponding reaction product.

Example 106

Ethyl 8-[4-(2-chlorophenyl)-1-piperazinyl]-8-oxooctanoate (**19f**)

The title compound was obtained from suberic acid monoethyl ester (**18c**) and 1-(2-chlorophenyl)piperazine (**17d**) (commercially available) using Method K, yield 80%. ^1H NMR ($CDCl_3$, HMDSO), δ: 1.13(t, J=7.0 Hz, 3H); 1.18-1.91(m, 8H); 2.29(t, J=6.0 Hz, 2H); 2.38(t, J=6.0 Hz, 2H); 3.02(t, J=5.0 Hz, 4H); 3.50-3.90(m, 4H); 4.11(q, J=7.0 Hz, 2H); 6.85-7.09(m, 2H); 7.14-7.48(m, 2H).

Example 107

Ethyl 8-[4-(3-chlorophenyl)-1-piperazinyl]-8-oxooctanoate (**19g**)

The title compound was obtained from suberic acid monoethyl ester (**18c**) and 1-(3-chlorophenyl)piperazine (**17e**) (commercially available) using Method K, yield 88%. ^1H NMR ($CDCl_3$, HMDSO), δ: 1.23(t, J=7.0 Hz, 3H); 1.18-1.79(m, 8H); 2.29(t, J=6.0 Hz, 2H); 2.36(t, J=6.0 Hz, 2H); 3.14(t, J=5.0 Hz, 4H); 3.44-3.87(m, 4H); 4.11(q, J=7.0 Hz, 2H); 6.66-6.92(m, 2H); 7.05-7.37(m, 2H).

Example 108

Ethyl 7-[4-(2-chlorophenyl)-1-piperazinyl]-7-oxoheptanoate (**19h**)

The title compound was obtained from pimelic acid monoethyl ester (**18a**) and 1-(2-chlorophenyl)piperazine (**17d**) (commercially available) using Method K, yield 79%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.23(t, J=7.0 Hz, 3H); 1.18-1.89(m, 6H); 2.29(t, J=6.0 Hz, 2H); 2.38(t, J=6.0 Hz, 2H); 3.00(t, J=5.0 Hz, 4H); 3.49-3.89(m, 4H); 4.12(q, J=7.0 Hz, 2H); 6.85-7.09(m, 2H); 7.14-7.48(m, 2H).

Example 109

Ethyl 7-[4-(3-chlorophenyl)-1-piperazinyl]-7-oxoheptanoate (**19i**)

The title compound was obtained from pimelic acid monoethyl ester (**18a**) and 1-(3-chlorophenyl)piperazine (**17e**) (commercially available) using Method K, yield 78%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.23(t, J=7.0 Hz, 3H); 1.18-1.89(m, 6H); 2.29(t, J=6.0 Hz, 2H); 2.36(t, J=6.0 Hz, 2H); 3.14(t, J=5.0 Hz, 4H); 3.45-3.89(m, 4H); 4.12(q, J=7.0 Hz, 2H); 6.67-6.94(m, 2H); 7.05-7.38(m, 2H).

Method L - General Synthesis of Amidoesters

A solution of dicarbonic acid monomethyl (or monoethyl) ester **18a-c** (2.75 mmol) in anhydrous dimethylformamide (3 mL) was cooled in ice bath under argon atmosphere and carbonyldiimidazole (490 mg, 3.01 mmol) was added. The mixture was stirred at ice bath temperature for 30 minutes and a solution of appropriate piperazine (2.75 mmol) in dimethylformamide (3 mL) was added (if the piperazine was used in a hydrochloride form triethylamine (1.0 mL) before the piperazine hydrochloride to the reaction mixture was added). The mixture was stirred at ice bath temperature for 1 hour followed by 20 hours at room temperature. Then the reaction mixture was diluted with brine (50 mL) and extracted with ethyl acetate (3 x 25 mL). The organic phase was washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was chromatographed on silica gel with appropriate eluent to give the corresponding reaction product.

Example 110

Ethyl 8-[4-(2-naphthoyl)-1-piperazinyl]-8-oxooctanoate (**19j**)

The title compound was obtained from suberic acid monoethyl ester (**18c**) and 2-naphthyl(1-piperazinyl)methanone (**13a**) using Method L, yield 79%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.16(t, J=7.0 Hz, 3H); 1.18-1.65(m, 8H); 2.25(t, J=6.0 Hz, 2H); 2.38(t, J=6.0 Hz, 2H); 3.36-3.65(m, 8H); 4.02(q, J=7.0 Hz, 2H); 7.43-7.74(m, 3H); 7.89-8.12(m, 4H).

Example 111

Ethyl 8-(4-benzoyl-1-piperazinyl)-8-oxooctanoate (**19k**)

The title compound was obtained from suberic acid monoethyl ester (**18c**) and phenyl(1-piperazinyl)methanone (**13h**) using Method L, yield 89%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.28(t, J=7.0 Hz, 3H); 1.14-1.83(m, 8H); 2.16(t, J=7.0 Hz, 2H); 2.23(t, J=7.0 Hz, 2H); 3.00-3.25(m, 4H); 3.49-3.83(m, 4H); 3.98(q, J=7.0 Hz, 2H); 7.39(s, 5H).

Example 112

Ethyl 8-{4-[4-(dimethylamino)benzoyl]-1-piperazinyl}-8-oxooctanoate (**19l**)

The title compound was obtained from suberic acid monoethyl ester (**18c**) and [4-(dimethylamino)phenyl](1-piperazinyl)methanone (**13i**) using Method L, yield 81%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.27(t, J=7.0 Hz, 3H); 1.15-1.88(m, 8H); 2.34(t, J=7.0 Hz, 2H); 2.52(t, J=6.0 Hz, 2H); 2.88(s, 6H); 3.00-3.21(m, 4H); 3.49-3.87(m, 4H); 4.11(q, J=7.0 Hz, 2H); 7.08(d, J=8.8 Hz, 2H); 7.35(s, 5H).

Example 113

Ethyl 8-[4-(4-methoxyphenyl)-1-piperazinyl]-8-oxooctanoate (**19m**)

The title compound was obtained from suberic acid monoethyl ester (**18c**) and 1-(4-methoxyphenyl)piperazine (**17f**) (commercially available) using Method L, yield 76%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.16(t, J=7.0 Hz, 3H); 1.05-1.76(m, 8H); 2.22(t, J=7.0 Hz, 2H); 2.29(t, J=7.0 Hz, 2H); 2.85-3.07(m, 4H); 3.43-3.78(m, 4H); 3.72(s, 3H); 4.05(q, J=7.0 Hz, 2H); 6.83(s, 4H).

Example 114

Ethyl 8-[4-(3-methoxyphenyl)-1-piperazinyl]-8-oxooctanoate (**19n**)

The title compound was obtained from suberic acid monoethyl ester (**18c**) and 1-(3-methoxyphenyl)piperazine (**17g**) (commercially available) using Method L, yield 62%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.29(t, J=7.0 Hz, 3H); 1.16-1.85(m, 8H); 2.16(t, J=7.0 Hz, 2H); 2.22(t, J=7.0 Hz, 2H); 3.00-3.25(m, 4H); 3.49-3.83(m, 4H); 3.65(s, 3H); 3.98(q, J=7.0 Hz, 2H); 6.36-6.67(m, 3H); 7.05-7.23(m, 1H).

Example 115

Ethyl 8-[4-(4-nitrophenyl)-1-piperazinyl]-8-oxooctanoate (**19o**)

The title compound was obtained from suberic acid monoethyl ester (**18c**) and 1-(4-nitrophenyl)piperazine (**17h**) (commercially available) using Method L, yield 67%. ^{1}H NMR ($CDCl_3$, HMDSO),δ: 1.23(t, J=7.0 Hz, 3H); 1.07-1.89(m, 8H); 2.29(t, J=7.0 Hz, 2H); 2.36(t, J=7.0 Hz, 2H); 3.25-3.92(m, 8H); 4.12(q, J=7.0 Hz, 2H); 6.83(d, J=8.8 Hz, 2H); 8.14(d, J=8.8 Hz, 2H).

Example 116

Methyl 8-{4-[2-(5-methoxy-1H-indol-3-yl)acetyl]-1-piperazinyl}-8-oxooctanoate (**19p**)

The title compound was obtained from suberic acid monomethyl ester (**18b**) and 2-(5-methoxy-1H-indol-3-yl)-1-(1-piperazinyl)-1-ethanone (**13b**) using Method L, yield 76%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.12-1.89(m, 8H); 2.29(t, J=7.0 Hz, 4H); 3.09-3.74(m, 8H); 3.65(s, 3H); 3.83(s, 2H); 3.85(s, 3H); 6.89(dd, J=8.8 and 3.0 Hz, 1H); 7.07(t, J=3.0 Hz, 2H); 7.16-7.35(m, 1H); 8.31(bs, 1H).

Example 117

Methyl 8-{4-[2-(2-naphthyloxy)ethyl]-1-piperazinyl}-8-oxooctanoate (**19r**)

The title compound was obtained from suberic acid monomethyl ester (**18b**) and 1-[2-(2-naphthyloxy)ethyl]piperazine (**16c**) using Method L, yield 56%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.14-1.81(m, 8H); 2.29(t, J=7.0 Hz, 4H); 2.43-2.69(m, 4H); 2.87(t, J=5.0 Hz, 2H); 3.32-3.74(m, 4H); 3.63(s, 3H); 4.23(t, J=5.0 Hz, 2H); 7.03-7.23(m, 2H); 7.29-7.52(m, 2H); 7.61-7.83(m, 2H).

Example 118

Ethyl 8-{4-[2-(1-naphthyloxy)acetyl]-1-piperazinyl}-8-oxooctanoate (**19s**)

The title compound was obtained from suberic acid monoethyl ester (**18c**) and 2-(1-naphthyloxy)-1-(1-piperazinyl)-1-ethanone (**13d**) using Method L, yield 65%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.23(t, J=7.0 Hz, 3H); 1.18-1.85(m, 8H); 2.27(t, J=7.0 Hz, 4H); 3.10-3.81(m, 8H); 3.92(s, 2H); 4.12(q, J=7.0 Hz, 2H); 7.32-7.59(m, 3H); 7.65-7.94(m, 4H).

Example 119

Methyl 8-{4-[2-(5-methoxy-1H-indol-3-yl)ethyl]-1-piperazinyl}-8-oxooctanoate (**19t**)

The title compound was obtained from suberic acid monomethyl ester (**18b**) and 5-methoxy-3-[2-(1-piperazinyl)ethyl]-1H-indole (**16b**) using Method L, yield 89%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.18-1.78(m, 8H); 2.34(t, J=7.0 Hz, 4H); 2.52(t, J=6.0 Hz, 4H); 2.65-2.89(m, 4H); 3.38-3.74(m, 4H); 3.67(s, 3H); 3.85(s, 3H); 6.87(dd, J=8.8 and 3.0 Hz, 1H); 7.03(t, J= 3.0 Hz, 2H); 7.25(d, J=8.8 Hz, 1H); 8.01(s, 1H).

Example 120

Ethyl 8-{4-[2-(1-benzothiophen-3-yl)acetyl]-1-piperazinyl}-8-oxooctanoate (**19u**)

The title compound was obtained from suberic acid monoethyl ester (**18c**) and 2-(1-benzothiophen-3-yl)-1-(1-piperazinyl)-1-ethanone (**13e**) using Method L, yield 83%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.23(t, J=7.0 Hz, 3H); 1.16-1.87(m, 8H); 2.29(t, J=7.0 Hz, 4H); 3.27-3.83(m, 8H); 3.94(s, 2H); 4.12(q, J=7.0 Hz, 2H); 7.18-7.52(m, 2H); 7.72-7.96(m, 2H).

Example 121

Ethyl 7-[4-(3,4-dichlorophenyl)-1-piperazinyl]-7-oxoheptanoate (**19y**)

The title compound was obtained from pimelic acid monoethyl ester (**18a**) and 1-(3,4-dichlorophenyl)piperazine (**17l**) (commercially available) using Method L, yield 73%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.23(t, J=7.0 Hz, 3H); 1.14-1.87(m, 6H); 2.16-2.49(m, 4H); 2.98-3.23(m, 4H); 3.47-3.83(m, 4H); 4.09(q, J=7.0 Hz, 2H); 6.74(dd, J=8.8 and 3.0 Hz, 1H); 6.96(d, J= 3.0 Hz, 1H); 7.32(d, J=8.8 Hz, 1H).

Example 122

Ethyl 7-[4-(4-fluorophenyl)-1-piperazinyl]-7-oxoheptanoate (**19v**)

The title compound was obtained from pimelic acid monoethyl ester (**18a**) and 1-(4-fluorophenyl)piperazine (**17j**) (commercially available) using Method L, yield 74%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.22(t, J=7.0 Hz, 3H); 1.16-1.89(m, 6H); 2.16-2.49(m, 4H); 2.93-3.18(m, 4H); 3.49-3.87(m, 4H); 4.09(q, J=7.0 Hz, 2H); 6.77-7.14(m, 4H).

Example 123

Ethyl 7-[4-(4-chlorophenyl)-1-piperazinyl]-7-oxoheptanoate (**19w**)

The title compound was obtained from pimelic acid monoethyl ester (**18a**) and 1-(4-chlorophenyl)piperazine (**17k**) (commercially available) using Method L, yield 75%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.23(t, J=7.0 Hz, 3H); 1.16-1.87(m, 6H); 2.16-2.49(m, 4H); 3.00-3.21(m, 4H); 3.49-3.87(m, 4H); 4.11(q, J=7.0 Hz, 2H); 6.85(d, J=8.8 Hz, 2H); 7.23(d, J=8.8 Hz, 2H).

Method M - Synthesis of O-Benzylhydroxamate Esters

To a solution of dicarbonic acid monoethyl (or monomethyl) ester **18a-c** (2.75 mmol) in anhydrous dichloromethane (10 mL) oxalyl chloride (0.84 mL, 9.63 mmol) and a drop of dimethylformamide were added, and the resulting mixture was stirred for 30 minutes at room temperature followed by 1 hour at 40°C. The solution was carefully evaporated under reduced pressure and the residue was dried in vacuum at 40°C. The resulting chloride was dissolved in anhydrous tetrahydrofuran (3 mL) and the obtained solution to a cold suspension (ice bath) of benzylhydroxylamine hydrochloride (2.75 mmol), tetrahydrofuran (10 mL), and saturated $NaHCO_3$ (10 mL) was added under vigorous stirring. The stirring was continued for 1 hour at ice bath temperature and 20 hours at room temperature. The mixture was diluted with brine (30 mL) and extracted with ethyl acetate (3 x 25 mL). The organic phase was washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel (20 g) with chloroform - ethyl acetate (gradient from 100:0 to 50:50) as eluent to give the corresponding reaction product (**20a-c**) in 80-90% yield.

Example 124

Ethyl 7-[(benzyloxy)amino]-7-oxoheptanoate (**20a**)

The title product was obtained from heptanedioic acid monoethyl ester, using Method M. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.22(t, J=7.0 Hz, 3H); 1.07-1.88(m, 6H); 1.89-2.26(m, 2H); 2.29(t, J=7.0 Hz, 2H); 4.11(q, J=7.0 Hz, 2H); 4.88(s, 2H); 7.31(s, 5H).

Example 125

Methyl 8-[(benzyloxy)amino]-8-oxooctanoate (**20b**)

The title product was obtained from octanedioic acid monomethyl ester, using Method M. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.09-1.83(m, 8H); 1.87-2.27(m, 2H); 2.27(t, J=7.0 Hz, 2H); 3.63(s, 3H); 4.87(s, 2H); 7.29(s, 5H).

Example 126

Ethyl 8-[(benzyloxy)amino]-8-oxooctanoate (**20c**)

The title product was obtained from octanedioic acid monoethyl ester, using Method M. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.23(t, J=7.0 Hz, 3H); 1.09-1.83(m, 8H); 1.87-2.27(m, 2H); 2.27(t, J=7.0 Hz, 2H); 4.12(q, J=7.0 Hz, 2H); 4.87(s, 2H); 7.29(s, 5H).

Method N - Synthesis of O-Benzylhydroxamate Carboxylic Acids

To a solution of appropriate ester **20a-c** (1,5-2 mmol) in tetrahydrofuran (5 mL), a saturated aqueous solution of LiOH (5 mL) was added. The mixture was stirred for 5 hours at room temperature. The organic volatiles were evaporated under reduced pressure and the mixture was supplemented with water (20 mL). The mixture was washed with diethyl ether and aqueous phase was acidified with 2 M HCl to pH 3. The crude product was extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with brine (3 x 10 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue was dried in vacuum to give expected product **21a** or **21b** in 60-70% yield.

Example 127

7-[(Benzyloxy)amino]-7-oxoheptanoic acid (**21a**),

The title product was obtained from ethyl 7-[(benzyloxy)amino]-7-oxoheptanoate (**20a**), using Method N. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.07-1.88(m, 6H); 1.89-2.26(m, 2H); 2.29(t, J=7.0 Hz, 2H); 4.88(s, 2H); 7.32(s, 5H).

Example 128

8-[(Benzyloxy)amino]-8-oxooctanoic acid (**21b**),

The title product was obtained from methyl 8-[(benzyloxy)amino]-8-oxooctanoate (**20b**) or ethyl 8-[(benzyloxy)amino]-8-oxooctanoate (**20c**), using Method N. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.09-1.81(m, 8H); 1.88-2.29(m, 2H); 2.27(t, J=7.0 Hz, 2H); 4.86(s, 2H); 7.30(s, 5H).

Method P - General Synthesis of O-Benzyl Hydroxamates

A solution of dicarbonic acid N-benzyloxy monoamide **21a** or **21b** (1 eq) in anhydrous dimethylformamide (2 mL/mmol) was cooled in ice bath under argon atmosphere, and carbonyldiimidazole (1.1 eq.) was added. The mixture was stirred at ice bath temperature for 30 minutes and a solution of appropriate piperazine (1 eq) in dimethylformamide (2 mL/mmol) was added (if the piperazine was used in a hydrochloride form, triethylamine (3 eq) was added to the reaction mixture prior to the piperazine hydrochloride). The mixture was stirred at ice bath temperature for 1 hour followed by 20 hours at room temperature. Then the reaction mixture was diluted with brine and extracted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was chromatographed on silica gel with appropriate eluent (chloroform - ethyl acetate for less polar and ethyl acetate - methanol for more polar compounds) to give the corresponding reaction product **22a-k**.

Example 129

N-(Benzyloxy)-8-[4-(4-cyanobenzoyl)-1-piperazinyl]-8-oxooctanamide (**22a**)

The title compound was obtained from 8-[(benzyloxy)amino]-8-oxooctanoic acid (**21b**) and 4-(1-piperazinylcarbonyl)benzonitrile (**13j**), using Method P, yield 79%. ^{1}H NMR ($CDCl_3$,

HMDSO), δ: 1.09-1.81(m, 8H); 1.87-2.17(m, 2H); 2.18-2.42(m, 2H); 3.32-3.69(m, 8H); 4.89(s, 2H); 7.38(s, 5H); 7.52(d, J=8.8 Hz, 2H); 7.76(d, J=8.8 Hz, 2H); 8.03(s, 1H).

Example 130

N-(Benzyloxy)-7-oxo-7-[4-(2-pyridinyl)-1-piperazinyl]heptanamide (**22b**)

The title compound was obtained from 7-[(benzyloxy)amino]-7-oxoheptanoic acid (**21a**) and 1-(2-pyridinyl)piperazine (**17l**) (commercially available), using Method P, yield 50%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.16-1.81(m, 6H); 2.36(t, J=7.0 Hz, 2H); 3.21(q, J=6.0 Hz, 2H); 3.36-3.85(m, 8H); 4.76(bs, 1H); 5.09(s, 2H); 6.58-6.74(m, 2H); 7.34(s, 5H); 7.41-7.63(m, 1H); 8.12-8.29(m, 1H).

Example 131

N-(Benzyloxy)-8-(4-{2-[4-(dimethylamino)phenyl]acetyl}-1-piperazinyl)-8-oxooctanamide (**22c**)

The title compound was obtained from 8-[(benzyloxy)amino]-8-oxooctanoic acid (**21b**) and 2-[4-(dimethylamino)phenyl]-1-(1-piperazinyl)-1-ethanone (**13k**), using Method P, yield 68%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.05-1.81(m, 8H); 1.85-2.32(m, 4H); 2.89(s, 6H); 3.07-3.69(m, 8H); 3.65(s, 2H); 4.87(s, 2H); 6.67(d, J=8.8 Hz, 2H); 7.07(d, J=8.8 Hz, 2H); 7.36(s, 5H); 8.00(s, 1H).

Example 132

N-(Benzyloxy)-8-oxo-8-[4-(2-pyrimidinyl)-1-piperazinyl]octanamide (**22d**)

The title compound was obtained from 8-[(benzyloxy)amino]-8-oxooctanoic acid (**21b**) and 2-(1-piperazinyl)pyrimidine (**17m**) (commercially available), using Method P, yield 64%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.14-1.81(m, 8H); 1.96-2.25(m, 2H); 2.36(t, J=7.0 Hz, 2H); 3.43-3.94(m, 8H); 4.89(s, 2H); 6.54(t, J=5.0 Hz, 1H); 7.38(s, 5H); 7.92-8.03(m, 1H); 8.32(d, J=5.0 Hz, 2H).

Example 133

N-(Benzyloxy)-8-(4-{3-[3-(dimethylamino)phenyl]propyl}-1-piperazinyl)-8-oxooctanamide (22e)

The title compound was obtained from 8-[(benzyloxy)amino]-8-oxooctanoic acid (21b) and N,N-dimethyl-3-[3-(1-piperazinyl)propyl]aniline (16k), using Method P, yield 63%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.18-1.83(m, 8H); 2.07-2.38(m, 4H); 2.43-2.76(m, 8H); 2.92(s, 6H); 3.38-3.80(m, 4H); 4.92(s, 2H); 6.71(d, J=8.8 Hz, 2H); 7.12(d, J=8.8 Hz, 2H); 7.41(s, 5H); 8.07-8.36(m, 1H).

Example 134

N-(Benzyloxy)-8-{4-[2-(2-naphthyloxy)acetyl]-1-piperazinyl}-8-oxooctanamide (22f)

The title compound was obtained from 8-[(benzyloxy)amino]-8-oxooctanoic acid (21b) and 2-(2-naphthyloxy)-1-(1-piperazinyl)-1-ethanone (13c), using Method P, yield 66%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.14-1.76(m, 8H); 1.94-2.40(m, 4H); 3.29-3.74(m, 8H); 4.83(s, 2H); 4.88(s, 2H); 7.07-7.30(m, 3H); 7.36(s, 5H); 7.31-7.58(m, 1H); 7.65-7.92(m, 3H); 8.25(bs, 1H).

Example 135

N-(Benzyloxy)-7-{4-[3-(1H-indol-3-yl)propanoyl]-1-piperazinyl}-7-oxoheptanamide (22g)

The title compound was obtained from 7-[(benzyloxy)amino]-7-oxoheptanoic acid (21a) and 3-(1H-indol-3-yl)-1-(1-piperazinyl)-1-propanone (13f), using Method P, yield 63%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.09-1.85(m, 6H); 1.92-2.41(m, 4H); 2.58-3.00(m, 4H); 3.05-3.72(m, 8H); 4.89(s, 2H); 6.91-7.39(m, 5H); 7.38(s, 5H); 7.52-7.74(m, 1H); 8.25-8.76(m, 1H).

Example 136

N-(Benzyloxy)-7-[4-(1H-indol-3-ylcarbonyl)-1-piperazinyl]-7-oxoheptanamide (22h)

The title compound was obtained from 7-[(benzyloxy)amino]-7-oxoheptanoic acid (21a) and 1H-indol-3-yl(1-piperazinyl)methanone (13g), using Method P, yield 69%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.14-1.78(m, 6H); 1.87-2.45(m, 4H); 3.34-3.78(m, 8H); 4.87(s, 2H); 7.14-7.54(m, 5H); 7.41(s, 5H); 7.58-7.83(m, 1H); 9.14-9.38(m, 1H).

Example 137

N-(Benzyloxy)-7-{4-[3-(1H-indol-3-yl)propyl]-1-piperazinyl}-7-oxoheptanamide (**22i**)

The title compound was obtained from 7-[(benzyloxy)amino]-7-oxoheptanoic acid (**21a**) and 3-[3-(1-piperazinyl)propyl]-1H-indole (**16f**), using Method P, yield 87%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.14-2.00(m, 8H); 2.12-2.56(m, 8H); 2.67-2.96(m, 4H); 3.32-3.71(m, 4H); 4.89(s, 2H); 6.92-7.36(m, 5H); 7.38(s, 5H); 7.49-7.69(m, 1H); 7.85-8.00(m, 1H).

Example 138

N-(Benzyloxy)-7-[4-(1H-indol-3-ylmethyl)-1-piperazinyl]-7-oxoheptanamide (**22j**)

The title compound was obtained from 7-[(benzyloxy)amino]-7-oxoheptanoic acid (**21a**) and 3-(1-piperazinylmethyl)-1H-indole (**16g**), using Method P, yield 59%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.16-1.87(m, 6H); 2.03-2.60(m, 8H); 3.32-3.69(m, 4H); 3.72(s, 2H); 4.89(s, 2H); 7.05-7.34(m, 5H); 7.38(s, 5H); 7.60-7.85(m, 1H); 8.03-8.41(m, 1H).

Example 139

N-(Benzyloxy)-7-[4-(3,4-dimethylphenyl)-1-piperazinyl]-7-oxoheptanamide (**22k**)

The title compound was obtained from 7-[(benzyloxy)amino]-7-oxoheptanoic acid (**21a**) and 1-(3,4-dimethylphenyl)piperazine (**17n**) (commercially available), using Method P, yield 71%. ^{1}H NMR ($CDCl_3$, HMDSO), δ: 1.14-1.80(m, 6H); 2.11(s, 3H) 2.16(s, 3H); 2.36-2.49(m, 4H); 3.36-3.85(m, 8H); 4.89(s, 2H); 6.70(dd, J=8.8 and 3.0 Hz, 1H); 6.86(d, J= 3.0 Hz, 1H); 7.02(d, J=8.8 Hz, 1H), 7.34(s, 5H).

Method Q - General Synthesis of Hydroxamic Acids from Amidoesters

To a 1 M solution of hydroxylamine hydrochloride in methanol (5 mL, 5 mmol) a 5 M solution of sodium methylate (1 mL, 5 mmol) was added, and the precipitate was filtered off. To the filtrate, a solution of appropriate amidoester (**19a-e**) (2.47 mmol) in methanol (3 mL) was added and the resultant mixture was stirred at room temperature for 24 hours. The mixture was acidified with acetic acid to pH 5 and the solvent was evaporated. The residue was extracted with ethyl acetate (50 mL), the extract was washed with water, brine, and dried ($MgSO_4$). The extract was filtrated, concentrated to ca. 5-10 mL, and allowed to crystallize. The precipitate was filtered, washed with ethyl acetate, and dried in vacuum to give the corresponding hydroxamic acid.

Example 140

8-Oxo-8-(4-phenyl-piperazin-1-yl)-octanoic acid hydroxyamide (**PX117402**)

The title compound was obtained from 8-oxo-8-(4-phenyl-piperazin-1-yl)-octanoic acid methyl ester (**19a**) by Method Q, yield 42%. M.p. 134-136°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.16-1.38 (m, 4H); 1.38-1.60 (m, 4H); 1.93 (t, 2H, J=7.4 Hz); 2.33 (t, 2H, J=7.2 Hz); 3.09 (m, 4H); 3.57 (m, 4H); 6.80 (t, 1H, J=7.1 Hz); 6.94 (d, 2H, J=8.0 Hz); 7.22 (t, 2H, J=7.7 Hz); 8.66 (s, 1H); 10.33 (s, 1H). HPLC analysis on Symmetry C_8 column: impurities 1.3% (column size 3.9 x 150 mm; mobile phase acetonitrile-0.1% H_3PO_4, 30:70; detector UV 220 nm; sample concentration 0.5 mg/ml; flow rate 1.1 mL/min). Anal. Calcd for $C_{18}H_{27}N_3O_3$, %: C 64.84, H 8.16, N 12.60. Found, %: C 64.71, H 8.20, N 12.52.

Example 141

7-(4-Benzhydryl-piperazin-1-yl)-7-oxo-heptanoic acid hydroxyamide (**PX117403**)

The title compound was obtained from ethyl 7-(4-benzhydryl-1-piperazinyl)-7-oxoheptanoate (**19b**) by Method Q, yield 29%. M.p. 157-159°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.08-1.32 (m, 2H); 1.35-1.60 (m, 4H); 1.82-2.02 (m, 2H); 2.03-2.40 (m, 6H); 3.23-3.60 (m, 4H overlapped with a water signal of DMSO); 4.30 (s, 1H); 7.09-7.52 (m, 10 H); 8.68 (s, 1H); 10.34 (s, 1H). HPLC analysis on Zorbax Rx-C_{18} column: impurities 1.5% (column size 4.6 x 150 mm; mobile phase acetonitrile-water, 80:20; detector UV 220 nm; sample concentration 1.0 mg/ml; flow rate 1.0 mL/min). Anal. Calcd for $C_{24}H_{31}N_3O_3$, %: C 70.39, H 7.63, N 10.26. Found, %: C 70.09, H 7.67, N 10.11.

Example 142

7-Oxo-7-(4-phenyl-piperazin-1-yl)-heptanoic acid hydroxyamide (**PX117404**)

The title compound was obtained from ethyl 7-oxo-7-(4-phenyl-1-piperazinyl)heptanoate (**19c**) by Method Q, yield 27%. M.p. 107-109°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.15-1.36 (m, 2H); 1.38-1.60 (m, 4H); 1.93 (t, 2H, J=7.1 Hz); 2.33 (t, 2H, J=7.3 Hz); 3.09 (m, 4H); 3.58 (m, 4H); 6.80 (t, 1H, J=7.3 Hz); 6.95 (d, 2H, J=8.2 Hz); 7.22 (t, 2H, J=7.9 Hz); 8.69 (s, 1H); 10.35 (s, 1H). HPLC analysis on Zorbax SB-C_{18} column: impurities 3% (column size 4.6 x 150 mm; mobile phase methanol-0.1% H_3PO_4, gradient from 50:50 to 90:10; detector UV 220 nm; sample concentration 0.55 mg/ml; flow rate 1.5 mL/min).

Anal. Calcd for $C_{17}H_{25}N_3O_3$, %: C 63.93, H 7.89, N 13.16. Found, %: C 63.80, H 7.89, N 13.06.

Example 143

8-(4-Benzhydryl-piperazin-1-yl)-8-oxo-heptanoic acid hydroxyamide (**PX117764**)

The title compound was obtained from methyl 8-(4-benzhydryl-1-piperazinyl)-8-oxooctanoate (**19d**) by Method Q, yield 32%. M.p. 126-129°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.14-1.30 (m, 4H); 1.34-1.54 (m, 4H); 1.91 (t, 2H, J=7.3 Hz); 2.15-2.32 (m, 6H); 3.38-3.50 (m, 4H); 4.30 (s, 1H); 7.17-7.50 (m, 10H); 8.66 (s, 1H); 10.32 (s, 1H). HPLC analysis on Symmetry C_8 column: impurities 3.3% (column size 3.9 x 150 mm; mobile phase acetonitrile - 0.1M phosphate buffer (pH 2.5), 50:50; detector UV 220 nm; sample concentration 0.5 mg/ml; flow rate 1.3 mL/min). Anal. Calcd for $C_{25}H_{33}N_3O_3$, %: C 70.89, H 7.85, N 9.92. Found, %: C70.81, H 7.63, N 10.11.

Example 144

8-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-8-oxo-octanoic acid hydroxyamide (**PX117768**)

The title compound was obtained from methyl 8-[4-(2-methoxyphenyl)-1-piperazinyl]-8-oxooctanoate (**19e**) by Method Q, yield 34%. M.p. 135-137°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.38 (m, 4H); 1.38-1.60 (m, 4H); 1.93 (t, 2H, J=7.3 Hz); 2.31 (t, 2H, J=7.2 Hz); 2.82-2.98 (m, 4H); 3.50-3.62 (m, 4H); 3.78 (s, 3H); 6.84-7.02 (m, 4H); 8.66 (s, 1H); 10.33 (s, 1H). HPLC analysis on Symmetry C_8 column: impurities <1.0% (column size 3.9 x 150 mm; mobile phase acetonitrile - 0.1M phosphate buffer (pH 2.5), 30:70; detector UV 220 nm; sample concentration 0.5 mg/ml; flow rate 1.1 mL/min). Anal. Calcd for $C_{19}H_{29}N_3O_4$, %: C 62.79, H 8.04, N 11.56. Found, %: C62.71, H 8.07, N 11.64.

Method R - General Synthesis of Hydroxamic Acids from Amidoesters

To a solution of amidoester **19f-w** (1 mmol) in methanol (3-5 mL), a solution of hydroxylamine hydrochloride (0.278 g, 4 mmol) in methanol (3 mL) followed by a solution of NaOH (0.320 g, 8 mmol) in water (1 mL) were added. After stirring for 15-45 minutes at ambient temperature, the reaction mixture was diluted with brine and extracted with ethyl acetate (3 x 30 mL). The organic phase was washed with brine, evaporated under reduced pressure by adding benzene to remove traces of water several times, and dried

in vacuum. The crude product was crystallized or chromatographed on silica gel to give the corresponding hydroxamic acid.

Example 145

8-[4-(2-Chloro-phenyl)-piperazin-1-yl]-8-oxo octanoic acid hydroxyamide (**PX118791**)

The title compound was obtained from methyl ethyl 8-[4-(2-chlorophenyl)-1-piperazinyl]-8-oxooctanoate (**19f**) using Method R. The crude product was crystallized from acetonitrile, yield 65%. M.p. 131-132°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.37(m, 4H); 1.40-1.60(m, 4H); 1.93(t, J=7.0 Hz, 2H); 2.33(t, J=7.3 Hz, 2H); 2.83-3.20(m, 4H); 3.53-3.66(m, 4H); 7.06(dt, J=1.6 and 7.8 Hz, 1H); 7.15(dd, J=1.4 and 8.2 Hz, 1H); 7.30(dt, J=1.4 and 8.2 Hz, 1H); 7.43(dd, J=1.6 and 7.8 Hz, 1H); 8.66(s, 1H); 10.33(s, 1H). HPLC analysis on Omnispher 5 C_{18} column: impurities <1% (column size 4.6 x 150 mm; mobile phase 45% acetonitrile + 55% 0.1M phosphate buffer (pH 2.5); detector UV 254 nm; sample concentration 1.0 mg/ml; flow rate 1.0 mL/min). Anal. Calcd for $C_{18}H_{26}ClN_3O_3 * 0.4H_2O$, %: C 57.64, H 7.20, N 11.20. Found, %: C 57.72, H 7.03, N 11.24.

Example 146

8-[4-(3-Chloro-phenyl)-piperazin-1-yl]-8-oxo octanoic acid hydroxyamide (**PX118792**)

The title compound was obtained from ethyl 8-[4-(3-chlorophenyl)-1-piperazinyl]-8-oxooctanoate (**19g**) using Method R. The crude product was crystallized from acetonitrile, yield 56%. M.p. 122-124°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.19-1.38(m, 4H); 1.40-1.61(m, 4H); 1.93(t, J=7.2 Hz, 2H); 2.29(t, J=7.4 Hz, 2H); 2.80-3.20(m, 4H); 3.55-3.66(m, 4H); 6.81(d, J=7.8 Hz, 1H); 6.87-6.99(m, 2H); 7.22(t, J=7.8 Hz, 1H); 8.65(d, J=1.4 Hz, 1H); 10.33(s, 1H). HPLC analysis on Zorbax SB C_{18} column: impurities ~2.5% (column size 4.6 x 150 mm; mobile phase acetonitrile-0.1M phosphate buffer (pH 2.5), gradient from 30:70 to 100:0; detector UV 254 nm; sample concentration 1.0 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{18}H_{26}ClN_3O_3$, %: C 58.77, H 7.12, N 11.42. Found, %: C 58.41, H 7.07, N 11.44.

Example 147

7-[4-(2-Chloro-phenyl)-piperazin-1-yl]-7-oxo heptanoic acid hydroxyamide (**PX118793**)

The title compound was obtained from ethyl 7-[4-(2-chlorophenyl)-1-piperazinyl]-7-oxoheptanoate (**19h**) using Method R. The crude product was crystallized from

acetonitrile, yield 62%. M.p. 128-130°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.17-1.36(m, 2H); 1.41-1.62(m, 4H); 1.94(t, J=7.0 Hz, 2H); 2.33(t, J=7.3 Hz, 2H); 2.80-3.20(m, 4H); 3.54-3.67(m, 4H); 7.06(dt, J=1.6 and 7.8 Hz, 1H); 7.15(dd, J=1.8 and 8.0 Hz, 1H); 7.30(dt, J=1.8 and 8.0 Hz, 1H); 7.43(dd, J=1.6 and 7.8 Hz, 1H); 8.67(d, J=1.8 Hz, 1H); 10.33(s, 1H). HPLC analysis on Omnispher 5 C_{18} column: impurities ~1.8% (column size 4.6 x 150 mm; mobile phase 40% acetonitrile + 60% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 1.0 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{17}H_{24}ClN_3O_3$, %: C 57.70, H 6.84, N 11.88. Found, %: C 57.76, H 6.87, N 11.79.

Example 148

7-[4-(3-Chloro-phenyl)-piperazin-1-yl]-7-oxo heptanoic acid hydroxyamide (**PX118794**)

The title compound was obtained from ethyl 7-[4-(3-chlorophenyl)-1-piperazinyl]-7-oxoheptanoate (**19i**) using Method R. The crude product was crystallized from acetonitrile, yield 48%. M.p. 120-122°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.17-1.34(m, 2H); 1.40-1.59(m, 4H); 1.93(t, J=7.3 Hz, 2H); 2.32(t, J=7.3 Hz, 2H); 3.07-3.24(m, 4H); 3.47-3.67(m, 4H); 6.80(dd, J=1.5 and 8.0 Hz, 1H); 6.86-6.98(m, 2H); 7.22(t, J= 7.8 Hz, 1H); 8.65(d, J=1.8 Hz, 1H); 10.33(s, 1H). HPLC analysis on Zorbax SB C_{18} column: impurities ~3% (column size 4.6 x 150 mm; mobile phase acetonitrile-0.1M phosphate buffer (pH 2.5), gradient from 30:70 to 100:0; detector UV 254 nm; sample concentration 0.5 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{17}H_{24}ClN_3O_3$, %: C 57.70, H 6.84, N 11.88. Found, %: C 57.74, H 6.86, N 11.79.

Example 149

8-[4-(Naphthalene-2-carbonyl)-piperazin-1-yl]-8-oxo octanoic acid hydroxyamide (**PX118830**)

The title compound was obtained from ethyl 8-[4-(2-naphthoyl)-1-piperazinyl]-8-oxooctanoate (**19j**) using Method R. The crude product was crystallized from acetonitrile, yield 54%. M.p. 133.5-134.5°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.20-1.60(m, 8H); 1.92(t, J=7.2 Hz, 2H); 2.20-2.40(m, 2H); 3.28-3.76(m, 8H); 7.50-7.66(m, 3H); 7.94-8.10(m, 4H); 8.66(d, J=1.6 Hz, 1H); 10.32(s, 1H). HPLC analysis on Alltima C_{18} column: impurities 3% (column size 4.6 x 150 mm; mobile phase 40% acetonitrile + 60% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 0.5 mg/ml; flow rate 1.3 mL/min). Anal. Calcd for $C_{23}H_{29}N_3O_4$, %: C 67.13, H 7.10, N 10.21. Found, %: C 66.90, H 7.09, N 10.23.

Example 150

8-(4-Benzoyl-piperazin-1-yl)-8-oxo octanoic acid hydroxyamide (**PX118831**)

The title compound was obtained from ethyl 8-(4-benzoyl-1-piperazinyl)-8-oxooctanoate (**19k**) using Method R. The crude product was crystallized from acetonitrile, yield 29%. M.p. 100-101°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.36(m, 4H); 1.38-1.58(m, 4H); 1.92(t, J=7.4 Hz, 2H); 2.30(t, J=6.6 Hz, 2H); 3.49(m, 8H); 7.38-7.50(m, 5H); 8.66(s, 1H); 10.32(s, 1H). HPLC analysis on Alltima C_{18} column: impurities 2.5% (column size 4.6 x 150 mm; mobile phase 20% acetonitrile + 80% 0.1M phosphate buffer (pH 2.5); detector UV 254 nm; sample concentration 1.0 mg/ml; flow rate 1.7 mL/min). Anal. Calcd for $C_{19}H_{27}N_3O_4$ * 0.35 H_2O, %: C 62.06, H 7.59, N 11.43. Found, %: C 62.03, H 7.50, N 11.33.

Example 151

8-[4-(4-Dimethylamino-benzoyl-piperazin-1-yl]-8-oxo octanoic acid hydroxyamide (**PX118832**)

The title compound was obtained from ethyl 8-{4-[4-(dimethylamino)benzoyl]-1-piperazinyl}-8-oxooctanoate (**19l**) using Method R. The crude product was crystallized from acetonitrile, yield 74%. M.p. 90-92°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.30(m, 4H); 1.40-1.60(m, 4H); 1.93(t, J=7.2 Hz, 2H); 2.30(t, J=7.0 Hz, 2H); 2.95(s, 6H); 3.44-3.52(m, 8H); 6.70(d, J=8.6 Hz, 2H); 7.29(d, J=8.6 Hz, 2H); 8.64(s, 1H); 10.32(s, 1H). HPLC analysis on Zorbax SB C_{18} column: impurities ~10% (column size 4.6 x 150 mm; mobile phase gradient 15 min 10% acetonitrile/90% 0.1M phosphate buffer (pH 2.5) – 100% 0.1M phosphate buffer; detector UV 254 nm; sample concentration 0.5 mg/ml; flow rate 1.0 mL/min). Anal. Calcd for $C_{21}H_{32}N_4O_4$ * 0.5 H_2O, %: C 61.00, H 8.04, N 13.55. Found, %: C 60.98, H 7.85, N 13.37.

Example 152

8-[4-(4-Methoxyphenyl)-piperazin-1-yl]-8-oxo octanoic acid hydroxyamide (**PX118846**)

The title compound was obtained from ethyl 8-[4-(4-methoxyphenyl)-1-piperazinyl]-8-oxooctanoate (**19m**) using Method R. The crude product was crystallized from acetonitrile, yield 48%. M.p. 149-150°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.33(m, 4H); 1.39-1.58(m, 4H); 1.93(t, J=7.2 Hz, 2H); 2.32(t, J=7.4 Hz, 2H); 2.88-3.03(m, 4H);

3.52-3.61(m, 4H); 3.68(s, 3H); 6.83(dt, J=9.6 and 2.8 Hz, 2H); 6.90(dt, J=9.6 and 2.8 Hz, 2H); 8.64(s, 1H); 10.32(s, 1H). HPLC analysis on Alltima C_{18} column: impurities 1.5% (column size 4.6 x 150 mm; mobile phase 25% acetonitrile + 75% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 0.5 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{19}H_{29}N_3O_4$, %: C 62.79, H 8.04, N 11.56. Found, %: C 62.65, H 8.09, N 11.53.

Example 153

8-[4-(3-Methoxyphenyl)-piperazin-1-yl]-8-oxo octanoic acid hydroxyamide (**PX118847**)

The title compound was obtained from ethyl 8-[4-(3-methoxyphenyl)-1-piperazinyl]-8-oxooctanoate (**19n**) using Method R. The crude product was crystallized from acetonitrile, yield 69%. M.p. 122-122.5°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.36(m, 4H); 1.39-1.58(m, 4H);1.93(t, J=7.0 Hz, 2H); 2.32(t, J=7.6 Hz, 2H); 3.03-3.17(m, 4H); 3.50-3.63(m, 4H); 3.71(s, 3H); 6.39(dd, J=8.0 and 2.0 Hz, 1H); 6.46(t, J=2.0 Hz, 1H); 6.52(dd, J=8.0 and 2.0 Hz, 1H); 7.12(t, J=8.0 Hz, 1H); 8.63(d, J=1.6 Hz, 1H); 10.31(s, 1H). HPLC analysis on Alltima C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase 25% acetonitrile + 75% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 0.5 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{19}H_{29}N_3O_4$, %: C 62.79, H 8.04, N 11.56. Found, %: C 62.65, H 8.06, N 11.43.

Example 154

N-Hydroxy-8-[4-(4-nitrophenyl)-1-piperazinyl]-8-oxooctanamide (**PX118849**)

The title compound was obtained from ethyl 8-[4-(4-nitrophenyl)-1-piperazinyl]-8-oxooctanoate (**19o**) using Method R. The crude product was crystallized from acetonitrile, yield 31%. M.p. 125-127°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.20-1.28 (m, 4H); 1.33-1.50(m, 4H); 1.93(t, J=7.6 Hz, 2H); 2.33(t, J=7.2 Hz, 2H); 3.40-3.70(m, 8H); 7.00(d, J=9.0 Hz, 2H); 8.07(d, J=9.0 Hz, 2H); 8.67(s, 1H); 10.33(s, 1H). HPLC analysis on Alltima C_{18} column: impurities 2.5% (column size 4.6 x 150 mm; mobile phase 40% acetonitrile + 60% 0.1M phosphate buffer (pH 2.5); detector UV 215 nm; sample concentration 0.5 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{18}H_{26}N_4O_5$, %: C 57.13, H 6.93, N 14.80. Found, %: C 57.06, H 6.94, N 14.72.

Example 155

N-Hydroxy-8-{4-[2-(5-methoxy-1H-indol-3-yl)acetyl]-1-piperazinyl}-8-oxooctanamide (**PX118927**)

The title compound was obtained from methyl 8-{4-[2-(5-methoxy-1H-indol-3-yl)acetyl]-1-piperazinyl}-8-oxooctanoate (**19p**) using Method R. The crude product was chromatographed on reverse phase Silasorb CL18 with methanol – 0.1% H_3PO_4 as eluent. The eluate was evaporated, the residue was dissolved in ethyl acetate, the extract was washed with water, evaporated, and dried. Yield 35%. Foam. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.13-1.32(m, 4H); 1.34-1.55(m, 4H); 1.91(t, J=7.3 Hz, 2H); 2.17-2.31(m, 2H); 3.24-3.57(m, 8H, overlapped with a signal of water); 3.73(s, 3H); 3.75(s, 2H); 6.71(dd, J=8.8 and 2.4 Hz, 1H); 7.05(d, J=2.4 Hz, 1H); 7.16(br s, 1H); 7.22(d, J=8.8 Hz, 1H); 8.67(s, 1H); 10.33(s, 1H); 10.75(s, 1H). HPLC analysis on Kromasil C_{18} column: impurities 5% (column size 4.6 x 150 mm; mobile phase 20% acetonitrile + 80% 0.2M acetate buffer (pH 5.0); detector UV 230 nm; sample concentration 1.0 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{23}H_{32}N_4O_5 * 0.25\ H_2O$, containing 4% of inorganic impurities, %: C 59.06, H 7.00, N 11.98. Found, %: C 59.01, H 7.02, N 11.97.

Example 156

N-Hydroxy-8-{4-[2-(2-naphthyloxy)ethyl]-1-piperazinyl}-8-oxooctanamide (**PX118930**)

The title compound was obtained from methyl 8-{4-[2-(2-naphthyloxy)ethyl]-1-piperazinyl}-8-oxooctanoate (**19r**) using Method R. The crude product was precipitated from diethyl ether, yield 35%. Foam. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.16-1.31(m, 4H); 1.37-1.54(m, 4H); 1.93(t, J=7.2 Hz, 2H); 2.27(t, J=7.4 Hz, 2H); 2.41-2.55(m, 4H, overlapped with a signal of DMSO); 2.79(t, J=5.9 Hz, 2H); 3.39-3.49(m, 4H); 4.21(t, J=5.9 Hz, 2H); 7.16(dd, J=8.8 and 2.4 Hz, 1H); 7.29-7.50(m, 3H); 7.76-7.86(m, 3H); 8.67(s, 1H); 10.33(s, 1H). HPLC analysis on Alltima C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase 25% acetonitrile + 75% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 1.0 mg/ml; flow rate 1.3 mL/min). Anal. Calcd for $C_{24}H_{33}N_3O_4 * 1.25\ H_2O$, %: C 64.05, H 7.95, N 9.34. Found, %: C 64.17, H 7.91, N 9.28.

Example 157

N-Hydroxy-8-{4-[2-(1-naphthyloxy)acetyl]-1-piperazinyl}-8-oxooctanamide (**PX118931**)

The title compound was obtained from ethyl 8-{4-[2-(1-naphthyloxy)acetyl]-1-piperazinyl}-8-oxooctanoate (**19s**) using Method R. The crude product was precipitated from diethyl ether, yield 34%. Foam. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.14-1.33(m, 4H); 1.37-1.56(m, 4H); 1.92(t, J=7.0 Hz, 2H); 2.21-2.36(m, 2H); 3.22-3.61(m, 8H, overlapped with a signal of H_2O); 3.92(s, 2H); 7.34-7.57(m, 3H); 7.80-7.95(m, 4H); 8.66(s, 1H); 10.32(s, 1H). HPLC analysis on Alltima C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase 50% acetonitrile + 50% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 1.0 mg/ml; flow rate 1.0 mL/min). Anal. Calcd for $C_{24}H_{31}N_3O_5$, %: C 65.29, H 7.08, N 9.52. Found, %: C 65.15, H 7.45, N 9.40.

Example 158

N-Hydroxy-8-{4-[2-(5-methoxy-1H-indol-3-yl)ethyl]-1-piperazinyl}-8-oxooctanamide oxalate (**PX118932**)

The title compound was obtained from methyl 8-{4-[2-(5-methoxy-1H-indol-3-yl)ethyl]-1-piperazinyl}-8-oxooctanoate (**19t**) using Method R. The crude product (ca. 0.33 mmol) was dissolved in abs. ethanol (1.5 mL) and a solution of oxalic acid dihydrate (0.1 g, 0.79 mmol) in abs. ethanol (1 mL) was added. The reaction mixture was stirred for 2 hours at ambient temperature, the precipitate was filtered and washed with diethyl ether. The product was crystallized from ethanol and dried, yield 70%. M.p. 122-125°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.17-1.35(m, 4H); 1.39-1.57(m, 4H); 1.93(t, J=7.6 Hz, 2H); 2.32(t, J=7.4 Hz, 2H); 2.93-3.17(m, 8H); 3.56-3.72(m, 4H); 3.77(s, 3H); 6.73(dd, J=8.8 and 2.2 Hz, 1H); 7.03(d, J=2.2 Hz, 1H); 7.16(d, J=2.2 Hz, 1H); 7.23(d, J=8.8 Hz, 2H); 10.35(s, 1H); 10.75(s, 1H). HPLC analysis on Zorbax SB C_{18} column: impurities ~7% (column size 4.6 x 150 mm; mobile phase 15 min gradient: acetonitrile-0.1M phosphate buffer (pH 2.5); 30/70 -100/0; detector UV 220 nm; sample concentration 0.5 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{23}H_{34}N_4O_4 * 1.3\ (COOH)_2$, %: C 56.15, H 6.74, N 10.23. Found, %: C 56.00, H 6.86, N 10.12.

Example 159

8-{4-[2-(1-Benzothiophen-3-yl)acetyl]-1-piperazinyl}-N-hydroxy-8-oxooctanamide (**PX118967**)

The title compound was obtained from ethyl 8-{4-[2-(1-benzothiophen-3-yl)acetyl]-1-piperazinyl}-8-oxooctanoate (**19u**) using Method R. The crude product was crystallized from acetonitrile, yield 35%. M.p. 140-141°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.15-1.34(m, 4H); 1.37-1.56(m, 4H); 1.92(t, J=7.3 Hz, 2H); 2.29(t, J=7.3 Hz, 2H); 3.36-3.60(m, 8H); 3.98(s, 2H); 7.34-7.44(m, 2H); 7.51(s, 1H); 7.78-7.85(m, 1H); 7.93-8.05(m, 1H); 8.65(s, 1H); 10.32(s, 1H). HPLC analysis on Omnispher 5 C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase 50% acetonitrile + 50% 0.1M phosphate buffer (pH 2.5); detector UV 215 nm; sample concentration 0.5 mg/ml; flow rate 1.3 mL/min). Anal. Calcd for $C_{22}H_{29}N_3O_4S$, %: C 61.23, H 6.77, N 9.74. Found, %: C 60.76, H 6.71, N 9.82.

Example 160

7-[4-(3,4-Dichlorophenyl)-1-piperazinyl]-N-hydroxy-7-oxoheptanamide (**PX118989**)

The title compound was obtained from ethyl 7-[4-(3,4-dichlorophenyl)-1-piperazinyl]-7-oxoheptanoate (**19y**) using Method R. The crude product was crystallized from ethyl acetate – methanol (9:1), yield 43%. M.p. 125-126°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.14-1.34(m, 2H); 1.38-1.59(m, 4H); 1.93(t, J=7.3 Hz, 2H); 2.32(t, J=7.0 Hz, 2H); 3.07-3.26(m, 4H); 3.48-3.63(m, 4H); 6.94(dd, J=8.8 and 2.9 Hz, 1H); 7.14(d, J=2.9 Hz, 1H); 7.40(d, J=8.8 Hz, 1H); 8.67(d, J=1.5 Hz, 1H); 10.33(s, 1H). HPLC analysis on Omnispher 5 C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase 40% acetonitrile + 60% 0.1M phosphate buffer (pH 2.5); detector UV 215 nm; sample concentration 1.0 mg/ml; flow rate 1.3 mL/min). Anal. Calcd for $C_{17}H_{23}Cl_2N_3O_3$, %: C 52.59, H 5.97, N 10.82. Found, %: C 52.50, H 5.90, N 10.75.

Example 161

7-[4-(4-Fluorophenyl)-1-piperazinyl]-N-hydroxy-7-oxoheptanamide (**PX118990**)

The title compound was obtained from ethyl 7-[4-(4-fluorophenyl)-1-piperazinyl]-7-oxoheptanoate (**19v**) using Method R. The crude product was crystallized from ethyl acetate – methanol (9:1), yield 29%. M.p. 119-120°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.34(m, 2H); 1.39-1.59(m, 4H); 1.93(t, J=7.3 Hz, 2H); 2.32(t, J=7.3 Hz, 2H); 2.94-

3.11(m, 4H); 3.51-3.62(m, 4H); 6.92-7.13(m, 4H); 8.67(s, 1H); 10.33(s, 1H). HPLC analysis on Alltima C_{18} column: impurities 2% (column size 4.6 x 150 mm; mobile phase 35% acetonitrile + 65% 0.1M phosphate buffer (pH 2.5); detector UV 254 nm; sample concentration 1.0 mg/ml; flow rate 1.0 mL/min). Anal. Calcd for $C_{17}H_{24}FN_3O_3$, %: C 60.52, H 7.17, N 12.45. Found, %: C 60.42, H 7.22, N 12.32.

Example 162

7-[4-(4-Chlorophenyl)-1-piperazinyl]-N-hydroxy-7-oxoheptanamide (**PX118991**)

The title compound was obtained from ethyl 7-[4-(4-chlorophenyl)-1-piperazinyl]-7-oxoheptanoate (**19w**) using Method R. The crude product was crystallized from ethyl acetate - methanol (9:1), yield 21%. M.p. 119-121°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.19-1.34(m, 2H); 1.39-1.59(m, 4H); 1.93(t, J=7.3 Hz, 2H); 2.33(t, J=7.3 Hz, 2H); 3.01-3.18(m, 4H); 3.50-3.64(m, 4H); 6.95(d, J=8.8 Hz, 2H); 7.24(d, J=8.8 Hz, 2H); 8.67(s, 1H); 10.33(s, 1H). HPLC analysis on Omnispher 5 C_{18} column: impurities 2.2% (column size 4.6 x 150 mm; mobile phase 35% acetonitrile + 65% 0.1M phosphate buffer (pH 2.5); detector UV 215 nm; sample concentration 1.0 mg/ml; flow rate 1.3 mL/min). Anal. Calcd for $C_{17}H_{24}ClN_3O_3$, %: C 57.70, H 6.84, N 11.88. Found, %: C 57.75, H 6.84, N 11.80.

Method S - General Synthesis of Hydroxamic Acids from O-benzyl Hydroxamates

To a solution of O-benzylhydroxamate **22a-k** (1 mmol) in methanol (5-10 mL), 5% palladium on activated carbon catalyst (0.050 g) was added and the black suspension was vigorously stirred under hydrogen atmosphere until initial compound disappeared. The reaction mixture was filtered through a small amount of silica gel (ca. 1-2 cm thin layer), the sorbent was washed with methanol, and the filtrate was evaporated in vacuum. The crude product was crystallized or chromatographed on silica gel to give the corresponding hydroxamic acid.

Example 163

8-[4-(4-Cyanobenzoyl)-piperazin-1-yl]-8-oxo octanoic acid hydroxyamide (**PX118844**)

The title compound was obtained from N-(benzyloxy)-8-[4-(4-cyanobenzoyl)-1-piperazinyl]-8-oxooctanamide (**22a**), using Method S, yield 74%. M.p. 150-150.5°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.38(m, 4H); 1.40-1.60(m, 4H); 1.92(t, J=7.0 Hz, 2H); 2.22-2.40(m, 2H); 3.20-3.70(m, overlapped with a signal of H_2O); 7.61(d, J=8.0 Hz, 2H);

7.94(d, J=8.0 Hz, 2H); 8.64(s, 1H); 10.32(s, 1H). HPLC analysis on Omnispher 5 C_{18} column: impurities 2% (column size 4.6 x 150 mm; mobile phase 20% acetonitrile + 80% 0.1M phosphate buffer (pH 2.5); detector UV 254 nm; sample concentration 0.5 mg/ml; flow rate 1.0 mL/min). Anal. Calcd for $C_{20}H_{26}N_4O_4 * 0.5\ H_2O$, %: C 60.74, H 6.88, N 14.17. Found, %: C 60.83, H 6.82, N 13.88.

Example 164

7-Oxo-7-(4-pyridin-2-yl-piperazin-1-yl]-heptanoic acid hydroxyamide oxalate (**PX118845**)

The title compound was obtained from N-(benzyloxy)-7-oxo-7-[4-(2-pyridinyl)-1-piperazinyl]heptanamide (**22b**), using Method S. The crude product (ca. 0.33 mmol) was dissolved in abs. ethanol (1.5 mL) and a solution of oxalic acid dihydrate (0.1 g, 0.79 mmol) in abs. ethanol (1 mL) was added. The reaction mixture was stirred for 2 hours at ambient temperature, the precipitate was filtered and washed with diethyl ether. The product was crystallized from ethanol and dried, yield 65%. M.p. 118-122°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.20-1.40(m, 2H); 1.42-1.65(m, 4H); 2.35(t, J=7.2 Hz, 2H); 2.77(t, J=7.2 Hz, 2H); 3.37-3.63(m, 8H); 6.65(dd, J=7.2 and 5.0 Hz, 1H); 6.83(d, J= 8.2 Hz, 1H); 7.55(ddd, J=8.2, 7.2 and 1.8 Hz, 1H); 8.11(dd, J= 5.0 and 1.8 Hz, 1H). HPLC analysis on Ultra Aqueous C_{18} column: impurities 2.3% (column size 4.6 x 150 mm; mobile phase 5% acetonitrile + 95% 0.1M phosphate buffer (pH 2.5); detector UV 215 nm; sample concentration 0.5 mg/mL; flow rate 1.5 mL/min). Anal. Calcd for $C_{16}H_{24}N_4O_3 * 0.5\ C_2H_2O_4 * 0.5\ H_2O$, %: C 54.53, H 7.00, N 14.96. Found, %: C 54.43, H 7.20, N 14.84.

Example 165

8-(4-{2-[4-(Dimethylamino)phenyl]acetyl}-1-piperazinyl)-N-hydroxy-8-oxooctanamide (**PX118848**)

The title compound was obtained from N-(benzyloxy)-8-(4-{2-[4-(dimethylamino)phenyl]acetyl}-1-piperazinyl)-8-oxooctanamide (**22c**), using Method S. The crude product was precipitated from diethyl ether, yield 63%. M.p. 77-79°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.34(m, 4H); 1.36-1.56(m, 4H); 1.92(t, J=7.2 Hz, 2H); 2.27(t, J=7.2 Hz, 2H); 2.85(s 6H); 3.25-3.50(m, 8H, overlapped with a signal of H_2O); 3.58(s, 2H); 6.66(d, J=8.2, 2H); 7.03(d, J=8.2 Hz, 2H); 8.65(s, 1H); 10.32(s, 1H). HPLC analysis on Alltima C_{18} column: impurities 4% (column size 4.6 x 150 mm; mobile phase 15% acetonitrile + 85% 0.1M phosphate buffer (pH 2.5); detector UV 215 nm; sample

concentration 0.5 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{22}H_{34}N_4O_4 * 0.5H_2O$, %: C 61.80, H 8.25, N 13.10. Found, %: C 61.90, H 8.18, N 13.11.

Example 166

N-Hydroxy-8-oxo-8-[4-(2-pyrimidinyl)-1-piperazinyl]octanamide (**PX118850**)

The title compound was obtained from N-(benzyloxy)-8-oxo-8-[4-(2-pyrimidinyl)-1-piperazinyl]octanamide (**22d**), using Method S. The crude product was crystallized from methanol, yield 37%. M.p. 132-133.5°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.36(m, 4H); 1.38-1.59(m, 4H); 1.93(t, J=7.3 Hz, 2H); 2.33(t, J=7.3 Hz, 2H); 3.46-3.58(m, 4H); 3.62-3.80(m, 4H); 6.65(t, J=4.8 Hz, 1H); 8.37(d, J=4.8 Hz, 2H); 8.65(br s, 1H); 10.29(br s, 1H). HPLC analysis on Alltima C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase 20% acetonitrile + 80% 0.1M phosphate buffer (pH 2.5); detector UV 230 nm; sample concentration 0.5 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{16}H_{25}N_5O_3$, %: C 57.30, H 7.51, N 20.88. Found, %: C 57.23, H 7.58, N 20.80.

Example 167

8-{4-[4-(Dimethylamino)phenethyl]-1-piperazinyl}-N-hydroxy-8-oxooctanamide (**PX118928**)

The title compound was obtained from N-(benzyloxy)-8-(4-{3-[3-(dimethylamino)phenyl]propyl}-1-piperazinyl)-8-oxooctanamide (**22e**), using Method S. The crude product was crystallized from acetonitrile, yield 45%. M.p. 103-105°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.11-1.33(m, 4H); 1.35-1.54(m, 4H); 1.92(t, J=7.2 Hz, 2H); 2.26(t, J=7.4 Hz, 2H); 2.24-2.66(m, 8H, partially overlapped with a signal of DMSO); 2.83(s, 6H); 3.25-3.50(m, 4H, partially overlapped with a signal of water); 6.64(d, J=8.6 Hz, 2H); 7.00(d, J=8.6 Hz, 2H); 8.67(s, 1H); 10.33(s, 1H). HPLC analysis on Alltima C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase 8% acetonitrile + 92% 0.1M phosphate buffer (pH 2.5); detector UV 215 nm; sample concentration 1.0 mg/ml; flow rate 1.3 mL/min). Anal. Calcd for $C_{22}H_{36}N_4O_3$, containing 1% of inorganic impurities, %: C 64.66, H 8.88, N 13.71. Found, %: C 64.64, H 8.94, N 13.70.

Example 168

N-Hydroxy-8-{4-[2-(2-naphthyloxy)acetyl]-1-piperazinyl}-8-oxooctanamide (**PX118929**)

The title compound was obtained from N-(benzyloxy)-8-{4-[2-(2-naphthyloxy)acetyl]-1-piperazinyl}-8-oxooctanamide (**22f**), using Method S. The crude product was crystallized from acetonitrile, yield 45%. M.p. 139-140.5°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.17-1.35(m, 4H); 1.37-1.56(m, 4H); 1.93(t, J=7.2 Hz, 2H); 2.32(t, J=7.0 Hz, 2H); 3.39-3.60(m, 8H, overlapped with a signal of H_2O); 4.97(s, 2H); 7.17-7.51(m, 4H); 7.37-7.89(m, 3H); 8.67(s, 1H); 10.34(s, 1H). TLC: single spot at R_f 0.3 (ethyl acetate-methanol, 4:1; detection - UV-254 nm). Anal. Calcd for $C_{24}H_{31}N_3O_5$, containing 1% of inorganic impurities, %: C 64.64, H 7.01, N 9.42. Found, %: C 64.64, H 6.96, N 9.45.

Example 169

N-Hydroxy-7-{4-[3-(1H-indol-3-yl)propanoyl]-1-piperazinyl}-7-oxoheptanamide (**PX118968**)

The title compound was obtained from N-(benzyloxy)-7-{4-[3-(1H-indol-3-yl)propanoyl]-1-piperazinyl}-7-oxoheptanamide (**22g**), using Method S. The crude product was crystallized from methanol – ethyl acetate (1:2), yield 40%. M.p. 152.5-153.5°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.13-1.33(m, 2H); 1.36-1.57(m, 4H); 1.92(t, J=7.0 Hz, 2H); 2.27(t, J=7.0 Hz, 2H); 2.67(t, J=7.3 Hz, 2H); 2.93(t, J=7.3 Hz, 2H); 3.25-3.52(m, 8H, overlapped with a signal of H_2O); 6.96(t, J=7.3 Hz, 1H); 7.05(t, J=7.3 Hz, 1H); 7.14(d, J=2.0 Hz, 1H); 7.33(d, J=7.3 Hz, 1H); 7.51(d, J=7.3 Hz, 1H); 8.67(s, 1H); 10.34(s, 1H); 10.78(s, 1H). HPLC analysis on Alltima C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase 20% acetonitrile + 80% 0.1M phosphate buffer (pH 2.5); detector UV 215 nm; sample concentration 0.25 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{22}H_{30}N_4O_4 * 0.5$ $H_2O * 0.1$ EtOAc, %: C 62.59, H 7.42, N 12.81. Found, %: C 62.61, H 7.35, N 12.92.

Example 170

N-Hydroxy-7-[4-(1H-indol-3-ylcarbonyl)-1-piperazinyl]-7-oxoheptanamide (**PX118969**)

The title compound was obtained from N-(benzyloxy)-7-[4-(1H-indol-3-ylcarbonyl)-1-piperazinyl]-7-oxoheptanamide (**22h**), using Method S. The crude product was crystallized from methanol – ethyl acetate (2:3), yield 52%. M.p. 86-88°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.16-1.35(m, 2H); 1.39-1.59(m, 4H); 1.93(t, J=7.3 Hz, 2H); 2.32(t, J=7.3 Hz, 2H); 3.43-3.70(m, 8H); 7.04-7.21(m, 2H); 7.44(dd, J=7.3 and 1.5 Hz, 1H); 7.66-7.75(m,

2H); 8.67(s, 1H); 10.34(s, 1H); 11.62(s, 1H). HPLC analysis on Omnispher 5 C_{18} column: impurities 2% (column size 4.6 x 150 mm; mobile phase 20% acetonitrile + 80% 0.1M phosphate buffer (pH 2.5); detector UV 215 nm; sample concentration 0.5 mg/ml; flow rate 1.3 mL/min). Anal. Calcd for $C_{20}H_{26}N_4O_4 * 0.5\ H_2O * 0.2\ CH_2Cl_2$, containing 2% of inorganic impurities, %: C 58.18, H 6.56, N 13.30. Found, %: C 58.12, H 6.54, N 13.33.

Example 171

N-Hydroxy-7-{4-[3-(1H-indol-3-yl)propyl]-1-piperazinyl}-7-oxoheptanamide (**PX118970**)

The title compound was obtained from N-(benzyloxy)-7-{4-[3-(1H-indol-3-yl)propyl]-1-piperazinyl}-7-oxoheptanamide (22i), using Method S. The crude product was crystallized from methanol – ethyl acetate (2:3), yield 23%. M.p. 165-166°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.11-1.32(m, 2H); 1.35-1.57(m, 4H); 1.79(t, J=7.3 Hz, 2H); 1.92(t, J=7.0 Hz, 2H); 2.18-2.41(m, 10H); 2.68(t, J=7.3 Hz, 2H); 3.42(br s, 4H); 6.90-7.06(m, 2H); 7.10(s, 1H); 7.31(d, J=7.3 Hz, 1H); 7.49(d, J=7.3 Hz, 1H); 8.66(s, 1H); 10.32(s, 1H); 10.74(s, 1H). HPLC analysis on μ Bondasphere Phenyl column: impurities 2.5% (column size 4.6 x 150 mm; mobile phase 20% acetonitrile + 80% 0.1M phosphate buffer (pH 2.5); detector UV 210 nm; sample concentration 0.5 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{22}H_{32}N_4O_3$, %: C 65.97, H 8.05, N 13.99. Found, %: C 65.85, H 8.10, N 13.97.

Example 172

N-Hydroxy-7-[4-(1H-indol-3-ylmethyl)-1-piperazinyl]-7-oxoheptanamide (**PX118978**)

The title compound was obtained from N-(benzyloxy)-7-[4-(1H-indol-3-ylmethyl)-1-piperazinyl]-7-oxoheptanamide (22j), using Method S. The crude product was crystallized from methanol – ethyl acetate (2:3), yield 52%. M.p. 65-67°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.10-1.30(m, 2H); 1.34-1.56(m, 4H); 1.91(t, J=7.3 Hz, 2H); 2.24(t, J=7.0 Hz, 2H); 2.23-2.50(m, 4H, overlapped with a signal of DMSO); 3.25-3.48(m, 4H, overlapped with a signal of water); 3.65(s, 2H); 6.97(t, J=7.3 Hz, 1H); 7.07(t, J=7.3 Hz, 1H); 7.23(s, 1H); 7.34(d, J=7.3 Hz, 1H); 7.63(d, J=7.3 Hz, 1H); 8.66(s, 1H); 10.32(s, 1H); 10.96(s, 1H). HPLC analysis on Omnispher C_{18} column: impurities 2% (column size 4.6 x 150 mm; mobile phase 15% acetonitrile + 85% 0.1M phosphate buffer (pH 2.5); detector UV 210 nm; sample concentration 0.5 mg/ml; flow rate 1.0 mL/min). Anal. Calcd for $C_{20}H_{28}N_4O_3 * 0.4\ H_2O * 0.25$ EtOAc, containing 4% of inorganic material, %: C 60.49, H 7.86, N 13.44. Found, %: C 60.65, H 7.43, N 13.39.

Example 173

7-[4-(3,4-Dimethylphenyl)-1-piperazinyl]-N-hydroxy-7-oxoheptanamide (**PX118994**)

The title compound was obtained from N-(benzyloxy)-7-[4-(3,4-dimethylphenyl)-1-piperazinyl]-7-oxoheptanamide (**22k**), using Method S. The crude product was crystallized from acetonitrile, yield 73%. M.p. 119.5-120.5°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.34(m, 2H); 1.39-1.59(m, 4H); 1.93(t, J=7.3 Hz, 2H); 2.11(s, 3H); 2.16(s, 3H); 2.32(t, J=7.3 Hz, 2H); 2.93-3.09(m, 4H); 3.49-3.61(m, 4H); 6.66(dd, J=8.8 and 2.2 Hz, 1H); 6.76(d, J=2.2 Hz, 1H); 6.97(d, J=8.8 Hz, 1H); 8.67(d, J=1.5 Hz 1H); 10.34(s, 1H). HPLC analysis on Alltima C_{18} column: impurities <2% (column size 4.6 x 150 mm; mobile phase 25% acetonitrile + 75% 0.1M phosphate buffer (pH 2.5); detector UV 210 nm; sample concentration 1.0 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{19}H_{29}N_3O_3$, %: C 65.68, H 8.41, N 12.09. Found, %: C 65.65, H 8.54, N 12.09.

Example 174

8-[4-(3-Fluorophenyl)-piperazin-I-yl]-8-oxooctanoic acid hydroxyamide (**PX118859**)

The title compound was obtained using methods analogous to those described above. M.p. 149-150.5°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.19-1.37(m, 4H); 1.39-1.58(m, 4H); 1.93(t, J=7.5 Hz, 2H); 2.32(t, J=7.4 Hz, 2H); 2.88-3.04(m, 4H); 3.54-3.65(m, 4H); 6.93-7.22(m, 4H); 8.65(br s, IH); 10.32(s, IH). HPLC analysis on Alltima C_{18}: ~1% impurities (column size 4.6x150mm; mobile phase 35% acetonitrile + 65% 0.1M phosphate buffer (pH 2.5); detector UV 220nm; sample concentration 0.5 mg/ml; flow rate 1.5 mL/min). Anal. Calcd. for $C_{18}H_{26}FN_3O_3$, %: C 61.52, H 7.46, N 11.96. Found, %: C 61.45, H 7.48, N 11.88

Example 175

8-Oxo-8-[4-(3-trifluoromethylphenyl)-piperazin-1-yl]-octanoic acid hydroxyamide (**PX118860**)

The title compound was obtained using methods analogous to those described above. M. p. 126-128°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.16-1.37(m, 4H); 1.38.1.59(m, 4H); 1.93(t, J=7.4 Hz, 2H); 2.33(t, J=7.0 Hz, 2H); 3.14.3.39(m, 4H, overlapped with a signal of water); 3.52-3.65(m, 4H); 7.09(d, J=7.6 Hz, IH); 7.18(s, IH); 7.22(d, J=8.4 Hz, IH); 7.43(t, J=8.0 Hz, IH); 8.64(s, IH); 10.32(s, IH). HPLC analysis on Omnispher 5 C_{18}: <1% impurities (column size 4.6 x 150 mm; mobile phase 40% acetonitrile + 60% 0.1M

phosphate buffer (pH 2.5); detector UV 254 nm; sample concentration 0.5 mg/ml; flow rate 1.5 mL/min). Anal. Calcd for $C_{19}H_{26}F_3N_3O_3$, %: C 56.85, H 6.53, N 10.47. Found, %: C 56.62, H 6.48, N 10.40.

Example 176

8-{4-[Bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-8-oxo octanoic acid hydroxyamide (**PX118898**)

The title compound was obtained using methods analogous to those described above. M.p. foam. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.16-1.35(m, 4H); 1.38-1.58(m, 4H); 1.91(t, J=7.4 Hz, 2H); 2.15-2.30(m, 6H); 3.52-3.65(m, 4H, overlapped with a signal of water); 4,39(s, 1H); 7.13(t, J=8.6 Hz, 4H); 7.44(dd, J=8.6 and 5.6 Hz, 4H); 8.65(br s, 1H); 10.31(br s, IH). HPLC analysis on Alltima C_{18}: ~3.5% impurities. (column size 4.6 x 150 mm; mobile phase 70% acetonitrile + 30% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 1.0 mg/ml; flow rate 1.3 mL/min). Anal. Calcd for $C_{25}H_{31}F_2N_3O_3$ * 0.25 H_2O, %: C 64.71, H 6.84, N 9.06. Found, %: C 64.50, H 6.81, N 8.90.

Example 177

8-(3-Methyl-4-m-tolyl-piperazin-1-yl)-8-oxo octanoic acid hydroxyamide (**PX118899**)

The title compound was obtained using methods analogous to those described above. M.p. 75- 76°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 0.82 and 0.90(d and d, J=6.6 Hz, 3H); 1.14-1.35(m, 4H); 1.39-1.59(m, 4H); 1.93(t, J=7.2 Hz, 2H); 2.24(s, 3H); 2. 13-2.42(m, 2H); 2.80-3.53(m, 5H, partly overlapped with a signal of H_2O); 3.62-4.31(m, 2H); 6.59(d, J=7.8 Hz, 1H); 6.69(d, J=7.8 Hz, IH); 6.72(s, 1H); 7.09(t, J=7.8 Hz, 1H); 8.65(s, 1H); 10.32(s, 1H). HPLC analysis on Omnispher 5 C_{18}: ~1.8% impurities (column size 4.6 x 150 mm; mobile phase 30% acetonitrile + 70% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 1.0 mg/ml; flow rate 1.2 mL/min). Anal. Calcd. for $C_{20}H_{31}N_3O_3$, %: C 66.45, H 8.64, N 11.62. Found, %: C 66.43, H 8.67, N 11.52.

Example 178

8-[4-(2-1H-Indol-3-yl-acetyl)-piperazin-l-yl]-8-oxo octanoic acid hydroxyamide (**PX118900**)

The title compound was obtained using methods analogous to those described above. M.p. foam. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.10-1.31(m, 4H); 1.34-1.56(m, 4H); 1.93(t,

J=7.2 Hz, 2H); 2.18-2.35(m, 2H); 3.20-3.58(m, 8H, overlapped with a signal of H_2O); 3.79(s, 2H); 6.96(t, J=7.0 Hz, 1H); 7.07(t, J=7.0 Hz, 1H); 7.21(s, 1H); 7.34(d, J=7.8 Hz, 1H); 7.55(d, J=7.8 Hz, 1H); 8.65(s, 1H); 10.32(s, 1H); 10.93(s, 1H). HPLC analysis on Alltima C_{18}: ~7.5% impurities (column size 4.6 x 150 mm; mobile phase 30% acetonitrile + 70% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 1.0 mg/ml; flow rate 1.0 mL/min). Anal. Calcd. for $C_{22}H_{30}N_4O_4$ * $0.1H_2O$ *0.1EtOAc., containing 3% of inorganic impurities, %: C 61.39, H 7.13, N 12.78. Found, %: C 61.45, H 7.08, N 12.81.

Example 179

8-(4-Diphenylacetyl-piperazin-l-yl)-8-oxo octanoic acid hydroxyamide **(PX118901)**

The title compound was obtained using methods analogous to those described above. M.p. foam. ^1H NMR (DMSO-d_6, HMDSO) δ: 1.14-l.30(m, 4H); 1.34-l.54(m, 4H); 1.93(t, J=7.2 Hz, 2H); 2.l7-2.32(m, 2H); 3.09-3.2l(m, 2H); 3.30-3.58(m, 6H, overlapped with a signal of H_2O); 5.55(s, 1H); 7.l5-7.37(m, 10H); 8.66(s, 1H); 0.33(s, lH). HPLC analysis on Omnispher 5 C_{18}: ~2.2% impurities. (column size 4.6 x 150 mm; mobile phase 60% acetonitrile + 40% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 0.5 mg/ml; flow rate 1.2 mL/min.) Anal Calcd for $C_{26}H_{33}N_3O_4$ * 0.5 MeOH, %: C 68.07, H 7.54, N 8.99. Found, %: C 68.04, H 7.23, N 8.99.

Example 180

8-[4-(2-Naphthalen-2-yl-acetyl)-piperazin-l-yl]-8-oxo octanoic acid hydroxyamide **(PX118902)**

The title compound was obtained using methods analogous to those described above. M. p. foam. ^1H NMR (DMSO-d_6, HMDSO) δ: 1.12-1.32(m, 4H); 1.35-1.56(m, 4H); 1.92(t, J=7.4 Hz, 2H); 2.28(t, J=6.8 Hz, 2H); 3.26-3.58(m, 8H, overlapped with a signal of H_2O); 3.91(s, 2H); 7.39(dd, J=8.4 and 1.8 Hz, 1H); 7.45-7.54(m, 2H); 7.73(s, 1H); 7.79-7.92(m, 3H); 8.67(s, 1H); 10.33(s, 1H). HPLC analysis on Alltima C_{18}: ~5% impurities (column size 4.6 x 150 mm;mobile phase 40% acetonitrile + 60% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 0.5 mg/ml; flow rate 1.3 mL/min.) Anal. Calcd. for $C_{24}H_{31}N_3O_4$ * 0.75 H_2O, %: C 65.66, H 7.46, N 9.57. Found, %: C 65.52, H 7.40, N 9.43.

Example 181

8-{4-[4-(1-Hydroxyimino-ethyl)-phenyl]-piperazin-1-yl}-8-oxo octanoic acid hydroxyamide (**PX118903**)

The title compound was obtained using methods analogous to those described above. M.p. 147-l47.5°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.18-1.35(m, 4H); 1.37-1.57(m, 4H); 1.93(t, J=7.4 Hz, 2H); 2.09(s, 3H); 2.33(t, J=7.2 Hz, 2H); 3.06-3.25(m, 4H); 3.51-3.65(m, 4H); 6.94(d, J=8.8 Hz, 2H); 7.51(d, J=8.8 Hz, 2H); 8.65(s, 1H); 10.32(s, IH); 10.86(s, 1H). HPLC analysis on Zorbax SB 5 C_{18}: ~5% of acetophenone derivative (sample contains ca. 5% of the corresponding methylketone 8-[4-(4-acetylphenyl)-1-piperazinyl]-N-hydroxy-8-oxooctanamide). (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), gradient 15 min from 20:80 to 100:0; detector UV 254 nm; sample concentration 0.5 mg/ml; flow rate 1.0 mL/min.) Anal. Calcd. for $C_{20}H_{30}N_4O_4$ containing 5% of the acetophenone $C_{20}H_{29}N_3O_4$, %: C 61.63, H 7.75, N 14.20. Found, %: C 61.67, H 7.76, N 13.76.

Example 182

8-Oxo-8[4-(3-phenylallyl)-piperazin-1-yl]-octanoic acid hydroxyamide (**PX118904**)

The title compound was obtained using methods analogous to those described above. M. p. foam. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.14-1.32(m, 4H); 1.36-1.55(m, 4H); 1.93(t, J=7.3 Hz, 2H); 2. 19-2.45(m, 6H); 3.10(d, J=6.6 Hz, 2H); 3.27-3.51(m, 4H, overlapped with a signal of H_2O); 6.29(dt, J=6.60 and 16.2 Hz, IH); 6.54(d, J=16.2 Hz, IH); 7. 15-7.48(m, 3H); 7.44(d, J=6.6 Hz, 2H); 8.67(br s, H); 10.33(s, IH). HPLC analysis on Alltima C_{18}: ~5% impurities (column size 4.6 x 150 mm; mobile phase 20% acetonitrile + 80% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 1.0 mg/ml; flow rate 1.5 mL/min.) Anal. Calcd. for $C_{21}H_{31}N_3O_3$ * 0.5 H_2O, %:
C 65.94, H 8.43, N 10.99. Found, %: C 66.05, H 8.28, N 10.94.

Example 183

8-[4-(2-Naphthalen-2-yl-ethyl)-piperazin-1-yl]-8-oxo octanoic acid hydroxyamide (**PX118908**)

The title compound was obtained using methods analogous to those described above. M. p. 118-120°C. 1H NMR (DMSO-d_6, HMDSO) δ: 1.16-1.34(m, 4H); 1.36-1.56(m, 4H); 1.92(t, J=7.3 Hz, 2H); 2.27(t, J=7.6 Hz, 2H); 2.34-2.55(m, 4H, overlapped with a signal of

DMSO); 2.63(t, J=8.4 Hz, 2H); 2.92(t, J=8.4 Hz, 2H); 3.28-3.52 (m, 4H, overlapped with a signal of H_2O); 7.37-7 .53(m, 3H); 7. 73(s, 1H); 7.77-7 .91(m, 3H); 8.67(s, 1H); 10.33(s, IH). HPLC analysis on Omnispher 5 C_{18}: ~1.5% impurities (column size 4.6 x 150 mm; mobile phase 25% acetonitrile + 75% 0.1M phosphate buffer (pH 2.5); detector UV 220 nm; sample concentration 0.5 mg/ml; flow rate 1.2 mL/min.) Anal. Calcd. for $C_{24}H_{33}N_3O_3$, %: C 70.04, H 8.08, N 10.21. Found, %: C 69.31, H 8.11, N 10.20.

Example 184

8-[4-(2,2-Diphenyl-ethyl)-piperazin-1-yl]-8-oxo octanoic acid hydroxyamide (**PX118909**)

The title compound was obtained using methods analogous to those described above. M. p. 117-118°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.12-1.31(m, 4H); 1.34-1.54(m, 4H); 1.91(t, J=7.4 Hz, 2H); 2.23(t, J=7.4 Hz, 2H); 2.31-2.48(m, 4H, overlapped with a signal of DMSO); 2.94(d, J=7.6 Hz, 2H); 3.26-3.48 (m, 4H, overlapped with a signal of H_2O); 4.26(t, J=7.6 Hz, 1H); 7.09-7.40(m, 10H); 8.65(s, 1H); 10.31(s, 1H). HPLC analysis on Alltima C_{18}: <1% impurities. (column size: 4.6 x 150 mm; mobile phase 25% acetonitrile + 75% 0.1M phosphate buffer (pH 2.5); detector UV 215 nm; sample concentration 1.0 mg/ml; flow rate 1.15 mL/min.) Anal. Calcd. for $C_{26}H_{35}N_3O_3$, %: C 71.37, H 8.06, N 9.60. Found, %: C 71.01, H 8.11, N 9.59.

Biological Activity

Candidate compounds were assessed for their ability to inhibit deacetylase activity (biochemical assays) and to inhibit cell proliferation (cell-based antiproliferation assays), as described below.

Primary Assay (1): Deacetylase Activity

Briefly, this assay relies on the release of radioactive acetate from a radioactively labelled histone fragment by the action of HDAC enzyme. Test compounds, which inhibit HDAC, reduce the yield of radioactive acetate. Signal (e.g., scintillation counts) measured in the presence and absence of a test compound provide an indication of that compound's ability to inhibit HDAC activity. Decreased activity indicates increased inhibition by the test compound.

The histone fragment was an N-terminal sequence from histone H4, and it was labelled with radioactively labelled acetyl groups using tritiated acetylcoenzyme A (coA) in conjunction with an enzyme which is the histone acetyltransferase domain of the transcriptional coactivator p300. 0.33 mg of peptide H4 (the N-terminal 20 amino acids of histone H4, synthesized using conventional methods) were incubated with His6-tagged p300 histone acetyltransferase domain (amino acids 1195-1673, expressed in *E. coli* strain BLR(DE3)pLysS (Novagen, Cat. No. 69451-3) and 3H-acetyl coA (10 µL of 3.95 Ci/mmol; from Amersham) in a total volume of 300 µL of HAT buffer (50 mM TrisCl pH 8, 5% glycerol, 50 mM KCl, 0.1 mM ethylenediaminetetraacetic acid (EDTA), 1 mM dithiothreitol (DTT) and 1 mM 4-(2-aminoethyl)-benzenesulfonylfluoride (AEBSF)). The mixture was incubated at 30°C for 45 min after which the His-p300 was removed using nickel-trinitriloacetic acid agarose (Qiagen, Cat No. 30210). The acetylated peptide was then separated from free acetyl coA by size exclusion chromatography on Sephadex G-15 (Sigma G-15-120), using distilled H_2O as the mobile phase.

After purification of the radiolabelled histone fragment, it was incubated with a source of HDAC (e.g., an extract of HeLa cells (a rich source of HDAC), recombinantly produced HDAC1 or HDAC2) and any released acetate was extracted into an organic phase and quantitatively determined using scintillation counting. By including a test compound with the source of HDAC, that compound's ability to inhibit the HDAC was determined.

Primary Assay (2): Deacetylase Activity: Fluorescent Assay

Alternatively, the activity of the compounds as HDAC inhibitors was determined using a commercially available fluorescent assay kit: (Fluor de Lys™, BioMol Research Labs, Inc., Plymouth Meeting, USA). HeLa extract was incubated for 1 hour at 37°C in assay buffer (25 mM HEPES, 137 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$, pH 8.0) with 15 µM acetylated substrate in the presence of test compound (HDAC inhibitor). The extent of deacetylation was determined by the addition of 50 µL of a 1-in-500 dilution of Developer, and measurement of the fluorescence (excitation 355 nm, emission 460 nm), according to the instructions provided with the kit.

Extensive comparative studies have shown that Primary Assay (1) and Primary Assay (2), discussed above, yield equivalent results. Primary Assay results reported herein are (a) exclusively from (1); (b) exclusively from (2); or (c) from both (1) and (2).

HeLa Cell Extract

The HeLa cell extract was made from HeLa cells (ATCC Ref. No. CCL-2) by freeze-thawing three times in 60 mM TrisCl pH 8.0, 450 mM NaCl, 30% glycerol. Two cell volumes of extraction buffer were used, and particulate material was centrifuged out (20800 g, 4°C, 10 min). The supernatant extract having deacetylase activity was aliquotted and frozen for storage.

Recombinantly Produced HDAC1 and HDAC2

Recombinant plasmids were prepared as follows.

Full length human HDAC1 was cloned by PCR using a λgt11 Jurkat cDNA library (Clontech-HL5012b). The amplified fragment was inserted into the EcoRI-SalI sites of pFlag-CTC vector (Sigma-E5394), in frame with the Flag tag. A second PCR was carried out in order to amplify a fragment containing the HDAC1 sequence fused to the Flag tag. The resulting fragment was subcloned into the EcoRI-Sac1 sites of the baculovirus transfer vector pAcHTL-C (Pharmingen-21466P).

Full length mouse HDAC2 was subcloned into pAcHLT-A baculovirus transfer vector (Pharmingen-21464P) by PCR amplification of the EcoRI-Sac1 fragment from a HDAC2-pFlag-CTC construct.

Recombinant protein expression and purification was performed as follows.

HDAC1 and HDAC2 recombinant baculoviruses were constructed using BaculoGold Transfection Kit (Pharmingen-554740). Transfer vectors were co-transfected into SF9 insect cells (Pharmingen-21300C). Amplification of recombinant viruses was performed according to the Pharmingen Instruction Manual. SF9 cells were maintained in serum-free SF900 medium (Gibco 10902-096).

For protein production, $2x10^7$ cells were infected with the appropriate recombinant virus for 3 days. Cells were then harvested and spun at 3,000 rpm for 5 minutes. They were then washed twice in PBS and resuspended in 2 pellet volumes of lysis buffer (25 mM HEPES pH 7.9, 0.1 mM EDTA, 400 mM KCl, 10% glycerol, 0.1% NP-40, 1 mM AEBSF). Resuspended cells were frozen on dry ice and thawed at 37°C 3 times and centrifuged for

10 minutes at 14,000 rpm. The supernatant was collected and incubated with 300 µl of 50% Ni-NTA agarose bead slurry (Qiagen-30210). Incubation was carried out at 4°C for 1 hour on a rotating wheel. The slurry was then centrifuged at 500 g for 5 minutes. Beads were washed twice in 1 ml of wash buffer (25 mM HEPES pH7.9, 0.1 mM EDTA, 150 mM KCl, 10% glycerol, 0.1% NP-40, 1 mM AEBSF). Protein was eluted 3 times in 300 µl elution buffer (25 mM HEPES pH 7.9, 0.1 mM EDTA, 250 mM KCl, 10% glycerol, 0.1% NP-40, 1 mM AEBSF) containing increasing concentrations of imidazole: 0.2 M, 0.5 M and 1 M. Each elution was performed for 5 minutes at room temperature. Eluted protein was kept in 50% glycerol at -70°C.

Assay Method

A source of HDAC (e.g., 2 µL of crude HeLa extract, 5 µL of HDAC1 or HDAC2; in elution buffer, as above) was incubated with 3 µL of radioactively labelled peptide along with appropriate dilutions of candidate compounds (1.5 µL) in a total volume of 150 µL of buffer (20 mM Tris pH 7.4, 10% glycerol). The reaction was carried out at 37°C for one hour, after which the reaction was stopped by adding 20 µL of 1 M HCl / 0.4 M sodium acetate. Then, 750 µL of ethyl acetate was added, the samples vortexed and, after centrifugation (14000 rpm, 5 min), 600 µL from the upper phase were transferred to a vial containing 3 mL of scintillation liquid (UltimaGold, Packard, Cat. No. 6013329). Radioactivity was measured using a Tri-Carb 2100TR Liquid Scintillation Analyzer (Packard).

Percent activity (% activity) for each test compound was calculated as:

$$\% \text{ activity} = \{ (S^C - B) / (S^\circ - B) \} \times 100$$

wherein S^C denotes signal measured in the presence of enzyme and the compound being tested, S° denotes signal measured in the presence of enzyme but in the absence of the compound being tested, and B denotes the background signal measured in the absence of both enzyme and compound being tested. The IC50 corresponds to the concentration which achieves 50% activity.

IC50 data for several compounds of the present invention, as determined using this assay, are also shown in Table 1, below.

Measurement of cell viability in the presence of increasing concentration of test compound at different time points is used to assess both cytotoxicity and the effect of the compound on cell proliferation.

Secondary Assay: Cell Proliferation

Compounds with HDAC inhibition activity, as determined using the primary assay, were subsequently evaluated using secondary cell-based assays. The following cell lines were used:

HeLa - Human cervical adenocarcinoma cell line (ATCC ref. No. CCL-2).

K11 – HPV E7 transformed human keratinocyte line provided by Pidder Jansen-Duerr, Institut für Biomedizinische Alternsforschung, Innsbruck, Austria.

NHEK-Ad – Primary human adult keratinocyte line (Cambrex Corp., East Rutherford, NJ, USA).

JURKAT – Human T-cell line (ATCC no. TIB-152).

Assay Method

Cells were cultured, exposed to candidate compounds, and incubated for a time, and the number of viable cells was then assessed using the Cell Proliferation Reagent WST-1 from Boehringer Mannheim (Cat. No. 1 644 807), described below.

Cells were plated in 96-well plates at 3-10x10^3 cells/well in 100 µL of culture medium. The following day, different concentrations of candidate compounds were added and the cells incubated at 37°C for 48 h. Subsequently, 10 µL/well of WST-1 reagent was added and the cells reincubated for 1 hour. After the incubation time, absorbance was measured.

WST-1 is a tetrazolium salt which is cleaved to formazan dye by cellular enzymes. An expansion in the number of viable cells results in an increase in the overall activity of mitochondrial dehydrogenases in the sample. This augmentation in the enzyme activity leads to an increase in the amount of formazan dye formed, which directly correlates to the number of metabolically active cells in the culture. The formazan dye produced is

quantified by a scanning multiwell spectrophotometer by measuring the absorbance of the dye solution at 450 nm wavelength (reference wavelength 690 nm).

Percent activity (% activity) in reducing the number of viable cells was calculated for each test compound as:

$$\% \text{ activity} = \{ (S^C - B) / (S^\circ - B) \} \times 100$$

wherein S^C denotes signal measured in the presence of the compound being tested, S° denotes signal measured in the absence of the compound being tested, and B denotes the background signal measured in blank wells containing medium only. The IC50 corresponds to the concentration which achieves 50% activity. IC50 values were calculated using the software package Prism 3.0 (GraphPad Software Inc., San Diego, CA) , setting top value at 100 and bottom value at 0.

IC50 data for several compounds of the present invention, as determined using this assay, are also shown in Table 2, below.

Measurement of cell viability in the presence of increasing concentration of test compound at different time points is used to assess both cytotoxicity and the effect of the compound on cell proliferation.

Screening in Mice with Intraperitoneal P388 Tumour

Female B6D2F1 hybrid mice weighing 19-23 grams were inoculated with the tumour cell line P388 (10^6 cells in 0.2 mL) intraperitoneally (IP). Inoculation of tumour cells was performed on a Friday and treatment with compounds at a dose of 64 µmol/kg/day started on Day 3 (Monday). The compounds were given as a single daily IP dose for five consecutive days. Compounds were dissolved in DMSO, at a concentration corresponding to 50 µL injection volume per treatment. Treatments were given at the same hour of the day (within one hour). Five mice in each group were treated with compounds, and with each series of experiments, control groups (not treated, and DMSO-treated) were included. Moribund mice were euthanised, and the day of death was recorded. Log-rank analysis of the survival data was performed using the statistical software SAS v8.1 (SAS Institute, Cary, NC, USA).

Biological Data

IC50 (or percent activity) data for several compounds of the present invention, as determined using the assays described above are summarised in Table 1 and Table 2, below.

The results of in vivo studies of mice with intraperitoneal P388 tumour for several compounds of the present invention, using the methods described above, are summarised in Table 3.

Table 1
Biochemical Assay Data

Compound		HDAC Inhibition (IC50 unless otherwise specified)		
No.	Ref.	HeLa	HDAC1	HDAC2
1	TSA	5 nM	15 nM	17 nM
2	SAHA	189 nM	-	-
3	PX117403	28% @ 500 nM	-	-
4	PX117404	35% @ 500 nM	-	-
5	PX117764	785 nM	-	-
6	PX117768	175 nM	-	-
7	PX118490	59% @ 100 nM	-	-
8	PX118491	47% @ 100 nM	-	-
9	PX118807	60% @ 100nM	-	-
10	PX118810	46 nM	-	-
11	PX118811	42 nM	-	-
12	PX118812	26 nM	-	-
13	PX118791	36 nM	-	-
14	PX118792	34 nM	-	-
15	PX118793	188 nM	-	-
16	PX118794	74 nM	-	-
17	PX118830	133 nM	-	-
18	PX118831	194 nM	-	-
19	PX118832	212 nM	-	-
20	PX118844	286 nM	-	-
21	PX118846	3.4 nM	-	-
22	PX118847	31 nM	-	-
23	PX118848	44% @100 nM	-	-
24	PX118849	26 nM	-	-
25	PX118850	70 nM	-	-

Table 2
Cell-Based Antiproliferation Assay Data

Compound		Cell Proliferation Inhibition WST-1 (IC50 unless otherwise specified)			
No.	Ref.	HeLa	K11	NHEK-AD	Jurkat
	TSA	350 nM	0.38 μM	0.2 μM	42 nM
	Oxamflatin	-	4.82 μM	3.53 μM	170 nM
	MS-275	-	9.16 μM	3.1 μM	365 nM
	SAHA	-	6.82 μM	5.37 μM	750 nM
1	PX117403	-	-	-	-
2	PX117404	-	-	-	-
3	PX117764	29.2 μM	9.45 μM	-	2.68 μM
4	PX117768	3.30 μM	8.67 μM	-	1.04 μM
5	PX118490	1.00 μM	2.49 μM	-	460 nM
6	PX118491	18 μM	8.24 μM	-	3.21 μM

Table 3
In Vivo Studies of Mice with Intraperitoneal P388 Tumour

Compound	Log rank statistic	Wilcoxon statistic	No. of mice
-	6.8173	1556.0	25
DMSO	6.4056	1290.0	20
PX118490	-3.3797	-654.0	5
PX118807	-4.6177	-750.0	5
PX118871	-3.4210	-605.0	5
PX118875	-3.0949	-525.0	5
PX118882	-4.9869	-613.0	5
PX118893	-3.5651	-725.0	5
PX118905	-4.0610	-565.0	5
PX118907	-4.1247	-817.0	5
PX118910	-9.6221	-869.0	5

* * *

The foregoing has described the principles, preferred embodiments, and modes of operation of the present invention. However, the invention should not be construed as limited to the particular embodiments discussed. Instead, the above-described embodiments should be regarded as illustrative rather than restrictive, and it should be appreciated that variations may be made in those embodiments by workers skilled in the art without departing from the scope of the present invention as set out in the appended claims.

REFERENCES

A number of patents and publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided herein. Each of these references is incorporated herein by reference in its entirety into the present disclosure.

Alpegiani et al., 1999, "Preparation of succinyl piperidinamides, morpholinamides, piperazinamides, and analogs as matrix metalloprotease inhibitors," published international (PCT) patent application number WO 99/02510, published 21 January 1999.

Andrews et al., 2000, Int. J. Parasitol., Vol. 30, No. 6, pp. 761-768.

Bair et al., 2002, "Deacetylase Inhibitors," published international (PCT) patent application number WO 02/22577, published 21 March 2002.

Barlaam et al., 2000, "Preparation of arylpiperazines as metalloproteinase inhibiting agents (MMP)," published international (PCT) patent application number WO 00/12478, published 9 March 2000.

Barlaam et al., 2001, "Preparation of arylpiperazines and arylpiperidines as metalloproteinase inhibiting agents," published international (PCT) patent application number WO 01/62751, published 30 August 2001.

Barta et al., 2000, "Synthesis and activity of selective MMP inhibitors with an aryl backbone," Bioorg. Med. Chem. Lett., Vol. 10, No. 24, pp. 2815-2817.

Baxter et al, 2000, "Preparation of hydroxamic acid derivatives as inhibitors of matrix metalloproteinses," published international (PCT) patent application number WO 00/69839, published 23 November 2000.

Baxter et al., 1999, "Hydroxamic and carboxylic acid derivatives having MMP and TNF inhibitory activity," published international (PCT) patent application number WO 99/24399, published 20 May 1999.

Bedell et al., 2000, "Preparation of hydroxamic acid derivatives as matrix metalloprotease inhibitors," published international (PCT) patent application number WO 00/69819, published 23 November 2000.

Bedell et al., 2001, "Preparation of sulfonyl aryl or heteroaryl hydroxamic acid compounds as inhibitors of matrix metalloproteinase," published international (PCT) patent application number WO 01/85680, published 15 November 2001.

Bernhard, D. et al., 1999, "Apoptosis induced by the histone deacetylase inhibitor sodium butyrate in human leukemic lymphoblasts," FASEB J., Vol. 13, No. 14, pp. 1991-2001.

Bernstein et al., 2000, Proc. Natl. Acad. Sci. USA, Vol. 97, No. 25, pp. 13708-13713.

Billedeau et al., 2000, "Preparation of amino acid sulfonamide hydroxamates as inhibitors of procollagen C-proteinase," published international (PCT) patent application number WO 00/37436, published 29 June 2000.

Billedeau RJ et al (2000) "Preparation of amino acid sulfonamide hydroxamates as inhibitors of procollagen C-proteinase." US patent US6492394.

Brehm, A., et al., 1998, "Retinoblastoma protein recruits histone deacetylase to repress transcription," Nature, 1998, Vol. 391, pp. 597-601.

Broadhurst et al., 1993, "Preparation of oxoheterocyclyl-substituted hydroxamic acid derivatives as collagenase inhibitors," published European patent application number EP 574 758, published 22 December 1993.

Broadhurst et al., 1995, "Hydroxamic acid derivatives with tricyclic substitution, usefulas collagenase inhibitors," published European patent application number EP 684 240 published 29 November 1995.

Buchwald, S.L., et al., 2000a, J. Org. Chem., Vol. 65, p. 1144;

Buchwald, S.L., et al., 2000b, J. Org. Chem., Vol. 65, p. 1158;

Buchwald, S.L., et al., 2001, J. Org. Chem., Vol. 66, p. 3820;

Chang et al., 2000, Nucleic Acids Res., Vol. 28, No. 20, pp. 3918-3925.

Chong L et al (2002) "Preparation of hydroxamic acid peptide deformylase inhibitors as antibacterial agents." Published PCT application WO0228829

Corneil et al., 1998, published Japanese patent application, publication number JP 10114681 A2.

Dangond et al., 1998, Biochem. Biophys. Res. Commun., Vol. 242, No. 3, pp. 648-652.

David, G., et al., 1998, Oncogene, Vol. 16(19), pp. 2549-2556.

Davie, J.R., 1998, "Covalent modifications of histones: expression from chromatic templates," Curr. Opin. Genet. Dev., Vol. 8, pp. 173-178.

De Crescenzo et al., 2000, "Preparation of sulfamato hydroxamic acid metalloprotease inhibitors," published international (PCT) patent application number WO 00/46221, published 10 August 2000.

Desai et al., 1999, Proc. AACR, Vol. 40, abstract #2396.

Emiliani, S., et al., 1998, "Characterization of a human RPD3 ortholog, HDAC3," Proc. Natl. Acad. Sci. USA, Vol. 95, p. 2795-2800.

Finnin et al., 1999, Nature, Vol. 401, pp. 188-193.

Fort, Y. et al., 2001, Tetrahedron, Vol. 57, p. 7657.

Furukawa et al., 1998, U.S. Patent No. 5834,249, "Process for production of protein," 10 November 1998.

Geerts et al., 1998, European patent publication no. EP 0 827 742 A1, published 11 March 1998.

Grozinger et al., 1999, Proc. Natl. Acad. Sci. USA, Vol. 96, pp. 4868-4873.

Hannah et al., 2001, "Preparation of hydroxamic acid derivatives," published international (PCT) patent application number WO 01/87870, published 22 November 2001.

Hartwig, J.F., et al., 1999, J. Org. Chem., Vol. 64, p. 5575.

Hoshikawa, Y., et al., 1994, Exp. Cell. Res., Vol. 214(1), pp. 189-197.

Hou et al., 2001, "Binding affinities for a series of selective inhibitors of gelatinase-A using molecular dynamics with a linear interaction energy approach," J. Phys. Chem. B, Vol. 105, No. 22, pp. 5304-5315.

Howe, L., et al., 1999, Crit. Rev. Eukaryot. Gene Expr., Vol. 9(3-4), pp. 231-243.

Iavarone et al., 1999, Mol. Cell Biol., Vol. 19, No. 1, pp. 916-922.

Kao et al., 2000, Genes & Dev., Vol. 14, p. 55-66.

Kijima et al., 1993, J. Biol. Chem., Vol. 268, pp. 22429-22435.

Kim et al., 1999, Oncogene, Vol. 18(15), pp. 2461-2470.

Kim et al., 2001, Nature Medicine, Vol. 7, No. 4, pp. 437-443.

Kim, M.S., et al., 2001 " Histone deacetylases induce angiogenesis by negative regulation of tumour suppressor genes," Nature Medicine, Vol 7. No. 4 pp. 437-443.

Kimura et al., 1994, Biol. Pharm. Bull., Vol. 17, No. 3, pp. 399-402.

Kitamura, K., et al., 2000, Br. J. Haematol., Vol. 108(4), pp. 696-702.

Kouzarides, T., 1999, "Histone acetylases and deacetylases in cell proliferation," Curr. Opin. Genet. Dev., Vol. 9, No. 1, pp. 40-48.

Kuusisto et al., 2001, Biochem. Biophys. Res. Commun., Vol. 280, No. 1, pp. 223-228.

Kwon et al., 1998, Proc. Natl. Acad. Sci. USA, Vol. 95, pp. 3356-3361.

Laherty, C.D., et al., 1997, Cell, Vol. 89(3), pp. 349-356.

Lea and Tulsyan, 1995; Anticancer Res., Vol. 15, pp. 879-883.

Lea et al., 1999, Int. J. Oncol., Vol. 2, pp. 347-352.

Lin, R.J., et al., 1998, Nature, Vol. 391(6669), pp. 811-814.

Martin et al., 2000, "Preparation of hydroxamic acid derivatives as proteinase inhibitors," published international (PCT) patent application number WO 00/12477, published 9 March 2000.

McCaffrey et al., 1997, Blood, Vol. 90, No. 5, pp. 2075-2083.

Mielnicki, L.M., et al., 1999, Exp. Cell. Res., Vol. 249(1), pp. 161-176.

Ng, H.H. and Bird, A., 2000, Trends Biochem. Sci., Vol. 25(3), pp. 121-126.

Niki et al., 1999, Hepatology, Vol. 29, No. 3, pp. 858-867.

Nokajima et al., 1998, Exp. Cell Res., Vol. 241, pp. 126-133.

Onishi et al., 1996, Science, Vol. 274, pp. 939-940.

Owen et al., 2000, "Preparation of hydroxamic acid carboxylic acid derivatives for treating conditions associated with matrix metalloproteinase, ADAM or ADAM-TS enzymes," published international (PCT) patent application number WO 00/56704, published 28 November 2000.

Owen et al., 2001, "Preparation of hydroxamic acid derivatives as matrix metalloprotease (MMP) inhibitors," published international (PCT) patent aplication number WO 01/44189, published 21 June 2001.

Pazin, M.J., et al., 1997, "What's up and down with histone deacetylation and transcription?," Cell, Vol. 89, No. 3, pp. 325-328.

Pratt et al., 2001, "Preparation of hydroxamic acid and N-formyl hydroxylamine derivatives as antibacterial agents," published international (PCT) patent application number WO 01/10834, published 15 February 2001.

Richon et al, 1996, Proc. Natl. Acad. Sci. USA, Vol. 93, pp. 5705-5708.

Richon et al., 1998, "A class of hybrid poler inducers of transformed cell differentiation inhibits histone deacetylases," Proc. Natl. Acad. Sci. USA, Vol. 95, pp. 3003-3007.

Saito et al., 1999, Proc. Natl. Acad. Sci. USA, Vol. 96, pp. 4592-4597.

Saunders, N. et al, 1999 "Histone deacetylase inhibitors as potential anti-skin cancer agents," Cancer Res., Vol. 59, No. 2 pp. 399-404.

Sonoda, H. et al., 1996, Oncogene, Vol. 13, pp. 143-149.

Spencer, V.A. and Davie, J.R., 1999, Gene, Vol. 240(1), pp. 1-12.

Suzuki et al., 1999, "Synthesis and histone deactylase inhibitory activity of new benzamide derivatives," J. Med. Chem., Vol. 42, pp. 3001-3003.

Takahashi et al., 1996, J. Antibiot. (Tokyo), Vol. 49, No. 5, pp. 453-457.

Takahashi, I., et al, 1996, "Selective inhibition of IL-2 gene expression by trichostatin A, a potent inhibitor of mammalian histone deacetylase," J. Antibiot. (Tokyo), Vol. 49, No. 5, pp. 453-457.

Tauton, J., et al., 1996, "A mammalian histone deacetylase related to the yeast transcriptional regulator Rpd3p," Science, Vol. 272, pp. 408-411.

Tsuji et al., 1976, J. Antibiot. (Tokyo), Vol. 29, No. 1, pp. 1-6.

Ueda, H., et al., 1994, J. Antibiot. (Tokyo), Vol. 47(3), pp. 315-323.

Van den Wyngaert et al., 2000, FEBS, Vol. 478, pp. 77-83.

Vigushin et al., 2001, Clin. Cancer Res., Vol. 7, No. 4, pp. 971-976.

Warrell et al., 1998, J. Natl. Cancer Inst., Vol. 90, pp. 1621-1625.

Watkins, C., et al., 2002a, "Carbamic acid compounds comprising a sulfonamide linkage as HDAC inhibitors," published international (PCT) patent application number WO 02/30879(PCT/GB01/04326) published 27 September 2002.

Watkins, C., et al., 2002b, "Carbamic acid compounds comprising an ether linkage as HDAC inhibitors," published international (PCT) patent application number WO 02/26703(PCT/GB01/04327) published 27 September 2002.

Watkins, C., et al., 2002c, "Carbamic acid compounds comprising an amide linkage as HDAC inhibitors," published international (PCT) patent application number WO 02/26696 (PCT/GB01/04329) published 27 September 2002.

Wong, J., et al., 1998, EMBO J., Vol. 17(2), pp. 520-534.

Yang, W.M., et al., 1996, "Transcriptional repression of YY1 is mediated by interaction with a mammalian homolog of the yeast global regulator RPD3," Proc. Natl. Acad. Sci. USA, Vol. 93, pp. 12845-12850.

Yang, W.M., et al., 1997, "Isolation and characterization of cDNAs corresponding to an additional member of the human histone deacetylase gene family," J. Biol. Chem., Vol 272, pp. 28001-28007.

Yoshida et al., 1995, Bioessays, Vol. 17, pp. 423-430.

Yoshida, M. and Horinouchi, S., 1999, Ann. N. Y. Acad. Sci., Vol. 886, pp. 23-36.

Yoshida, M., Beppu, T., 1988, "Reversible arrest of proliferation of rat 3Y1 fibroblasts in both G1 and G2 phases by trichostatin A," Exp. Cell. Res., Vol. 177, pp. 122-131.

Yoshida, M., et al., 1990a, J. Biol. Chem., Vol. 265(28), pp. 17174-17179.

Yoshida, M., et al., 1990b, J. Antibiot. (Tokyo), Vol. 43(9), pp. 1101-1106.